VOLUME 84 NUMBER 6

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DECEMBER 1949

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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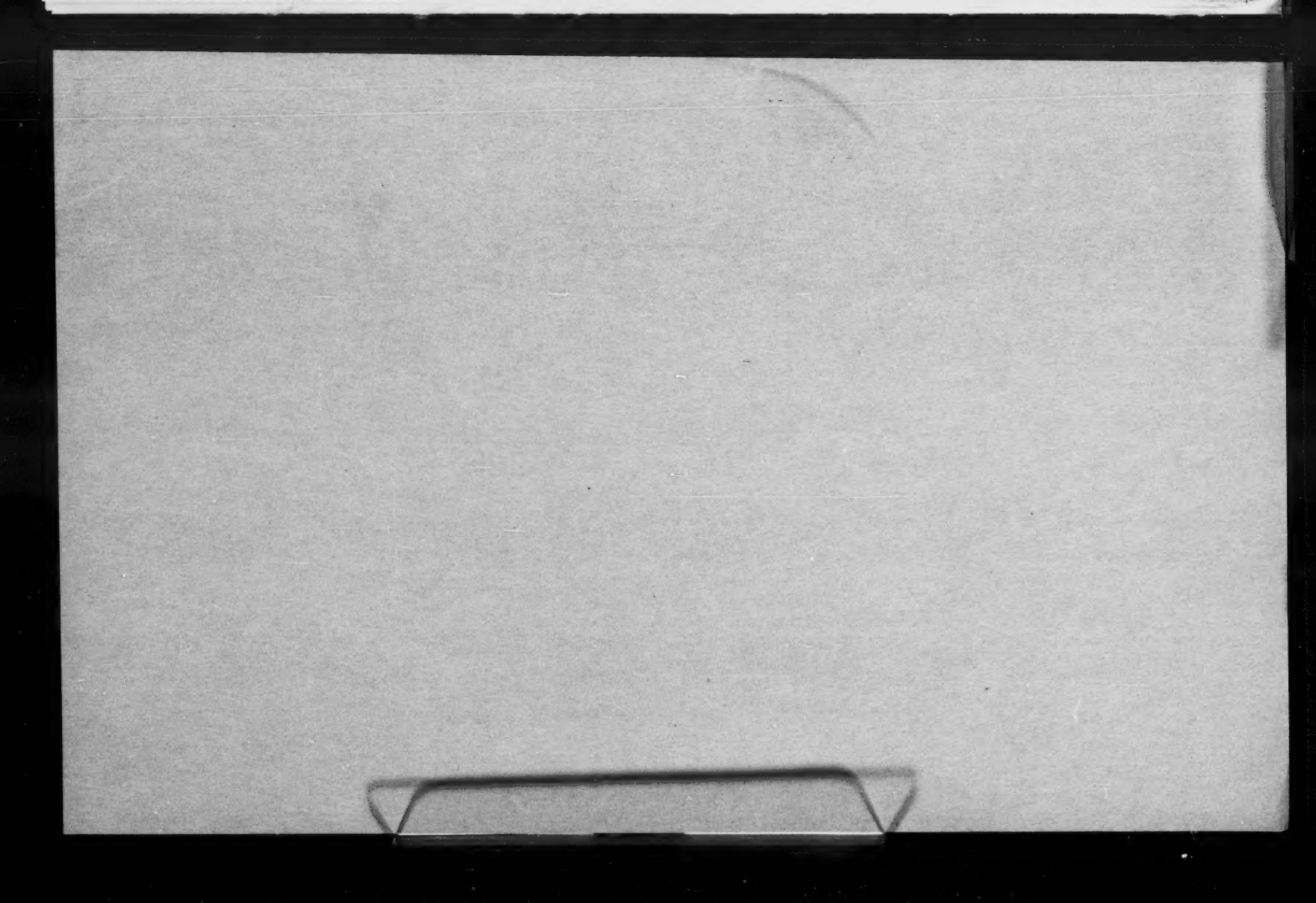

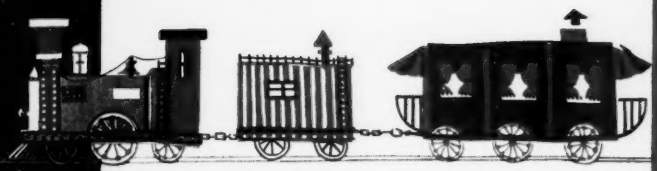

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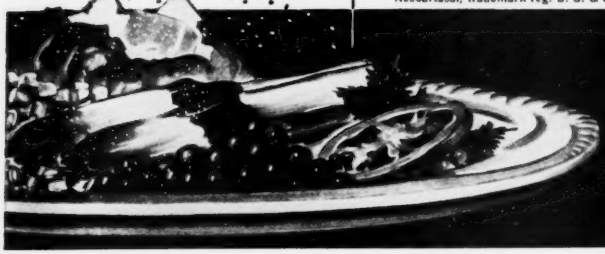

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Donovan, M. A.: New York State J. Med. 45:1756 (Aug. 15) 1945.

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  Chapman, D. W. and Shaffer, C. F.: Arch. Internal Med. 79:449, 1947.

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  Weiser, F. A.: Grace Hospital Bulletin, Detroit (Jan.) 1947, p. 25.

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VOLUME 84
1949

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
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VOLUME 84 DECEMBER 1949 NUMBER 6

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TUSSIVE SYNCOPE

Observations on the Disease Formerly Called Laryngeal Epilepsy, with Report of Two Cases

WILLIAM S. McCANN, M.D.

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AND

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JOHN J. KELLY, M.D.

ROCHESTER, N. Y.

IN 1876, Charcot [1] described the syndrome of laryngeal vertigo,[2] characterized by the loss of consciousness after severe coughing. Since then, occasional cases have been described, and in some instances the unusual vigor of coughing, associated with a respiratory infection, such as pertussis, may have been important. Whitty [3] reviewed nearly 100 of these cases in 1943, adding 4 more, and stated that he felt that epilepsy was an important factor despite rather meager evidence. He quoted De Havilland Hall, who in 1894 called attention to the large number of middle-aged plethoric males with laryngitis or bronchitis in a series of these cases. Wilkins and Friedland [4] observed that some normal subjects could lose consciousness by performing the Valsalva

From the Chest Laboratory, Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical, Surgical and Psychiatric Clinics, Strong Memorial Hospital and Rochester Municipal Hospital.

1. Charcot, J. M.: Statement to the Société de Biologie, Nov. 19, 1876, Gaz. méd. de Paris **5**:588, 1876; Description of "la grande attaque hystérique," Progr. méd. **7**:17, 1879.

2. In 1679, Thomas Sydenham (cited by Major, R. H.: Classic Descriptions of Disease, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 201) described the severe cough of patients seen in an epidemic of respiratory disease resembling influenza and noted that ". . . the cough occasioned such violent motion of the lungs, that sometimes a vomiting and vertigo ensued."

3. Whitty, C. W. M.: On the So-Called "Laryngeal Epilepsy," Brain **66**:43, 1943.

4. Wilkins, R. W., and Friedland, C. K.: Laryngeal Epilepsy Due to Increased Intrathoracic Pressure, J. Clin. Investigation **23**:939, 1944.

experiment of forced expiration against a closed glottis; in addition, diminished venous return and cardiac output were recorded by the ballistocardiographic method. The authors described 2 patients with pulmonary disease with similar signs; in 1 of them voluntary coughing could produce loss of consciousness. In 1946, Rook [5] observed 3 examples of syncope due to coughing in 500 cases of loss of consciousness in personnel of the Royal Air Force and questioned the importance of epilepsy, favoring the concept of cerebral congestion and anoxia instead.

Three more cases of this syndrome have been recorded recently; the first 2 are described in detail in this paper. The third patient could not be studied by cardiac catheterization because of pulmonary embolism from thrombophlebitis in the legs. However, the association of syncopal attacks with coughing made possible the presumptive diagnosis of tussive syncope.

REPORT OF CASES

CASE 1.—A male schoolteacher of 42 had had repeated episodes of fainting associated with coughing for the past three years. On some occasions he had fallen, once fracturing some ribs, whereas with less severe coughing he usually became lightheaded and confused and felt tingling of the hands and feet. He had occasionally been observed to have a brief clonic convulsion; complete loss of consciousness did not occur while he was recumbent, however. He had smoked two to three packs of cigarets daily for years and ingested large quantities of coffee.

Physical Examination.—The patient was a short man with a moderately obese abdomen. There was some tachypnea with a rate of 20 to 30 respirations per minute, but no evidence of orthostatic hypotension as the recumbent blood pressure of 115 systolic and 88 diastolic rose to 122 systolic and 90 diastolic on standing. The voice was husky, and the nasopharynx was chronically congested. Chest expansion was slightly limited, and the bronchovascular markings in the roentgenogram of the chest were more prominent than usual. The results of studies of the blood, glucose tolerance tests and lumbar puncture were all normal, as were the electroencephalogram and electrocardiogram. Neither massage of the carotid sinus, hyperventilation nor venous congestion of the head produced by a pressure cuff around the neck at 50 mm. of mercury caused syncope. Performance of the Valsalva maneuver of forced expiration against a closed glottis caused congestion of the face and head, disappearance of heart sounds and inability to obtain the blood pressure, followed within fifteen seconds by a grand mal convulsion.

Laboratory Examination.—Studies done in the chest laboratory demonstrated a mild degree of pulmonary insufficiency. Fluoroscopic examination of the chest showed decreased diaphragmatic excursion, and the total volume of the lungs was found to be reduced to 85 per cent of the predicted value, whereas the volume of residual air was 30 per cent of the total capacity (table 1). Slight hypoxemia was shown by the reduction of the arterial oxygen tension to 79 mm. and the oxygen saturation to 93.6 per cent. During an exercise tolerance test [6] there was considerable hyperventilation and diminished respiratory efficiency

5. Rook, A. F.: Coughing and Unconsciousness: The So-Called Laryngeal Epilepsy, Brain **69**:138, 1946.

6. Bruce, and others: Normal Respiratory and Circulatory Pathways of Adaptation in Exercise, J. Clin. Investigation; to be published.

(fig. 1). The ballistocardiogram was abnormal in pattern and irregular in amplitude except after the patient was exposed to cold or after the Müller experiment. Under these circumstances there was marked bradycardia with a rate of 52 to 60 beats per minute.

A cinefluorogram, obtained at the rate of 60 frames per second for five seconds during a paroxysm of coughing, showed appreciable bulging of the right atrium, the venae cavae and the pulmonary conus and greater density of the hilar root shadows, attributed to the momentary "trapping" of blood within the pulmonary circulation (fig. 2).[7]

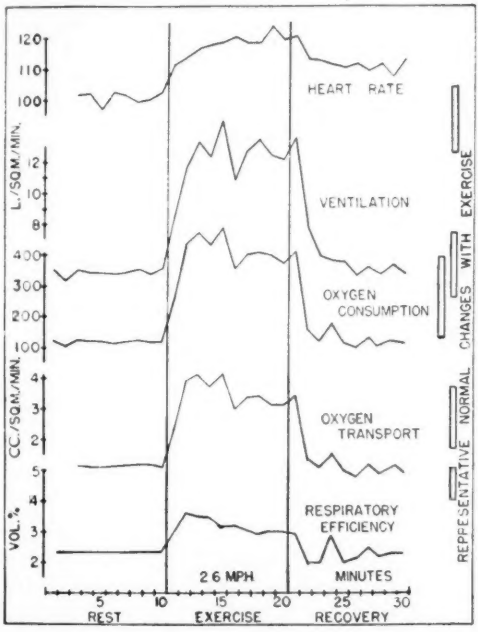

Fig. 1.—Exercise tolerance in case 1. Note the tachycardia, hyperventilation and decreased respiratory efficiency (volumes per cent of oxygen absorbed from room air) throughout the test.

On another occasion, with an indwelling needle in the femoral artery, a prompt transient rise in pressure occurred in the Valsalva maneuver, followed by a marked drop in pressure which persisted for several seconds until climaxed by a convulsion (fig. 3*C*). The electrocardiogram revealed no asystole during this interval.

Cardiac catheterization not only showed the usual decrease in net pulse pressure in the right ventricle in the Valsalva maneuver (fig. 3*B*), with a reduction in systemic pulse pressure, but also revealed the extraordinary pressures that could develop inside the right ventricle during a paroxysm of coughing (fig. 3*A*).

7. The cinefluorogram was made in the department of radiology.

TABLE 1.—*Laboratory Data in Case 1*

	Value Predicted from Height	Value Observed	Value Observed / Value Predicted × 100, %
Lung Volumes			
Vital capacity	3.80 L.	2.90 L.	76
Residual air	1.13 L.	1.27 L.	112
Total capacity	4.93 L.	4.17 L.	85
Residual air	23%	30%	..
Venous Pressure			
Patient recumbent, resting: 9.6 cm. (no increase with pressure over right upper quadrant of abdomen)			
Patient recumbent, following ambulatory activity: 16.7 cm. (increased to 18.7 cm. with vigorous coughing)			
Circulation Times			
Arm to tongue, with ether..... 18 sec.			
Arm to mouth, with macasol [18].... 18 sec.			

Catheterization Studies	1	2	3
Arterial blood			
Tension, mm			
CO_2	42	..	38
O_2	79	..	73
Content, vol. %			
CO_2	42.4	..	43.7
O_2	18.0	..	16.5
Venous blood			
Tension, mm.			
CO_2	40	49	48
O_2	38	32	38
Content, vol. %			
CO_2	43.2	47.5	46.9
O_2	13.4	10.4	12.5
Arterioventicular difference, vol. %	4.6	..	4.34
O_2 consumption, cc./min.	218	186	197
Cardiac output, L./min.	4.75	..	4.34
O_2 capacity, vol. %	19.20	..	18.44
O_2 saturation of arterial blood, %	93.8	..	89.5
Maximum systolic pressure in right ventricle, patient resting, mm.	28	41	17

Many pressures over 200 mm. were observed,[8] as in other patients (fig. 4); the maximal pressure recorded in this patient was 300 mm. Significantly high pressures

8. That the coughing pressures observed were not artefacts in recording may be seen from the calibrations (fig. 3), revealing no overshooting of a fixed pressure, and from the records of coughing obtained during cardiac catheterization of other patients (fig. 4). None of these patients experienced tussive syncope at any time, and the maximal pressures in the right ventricle or the pulmonary artery during coughing ranged from 50 to 150. The values reported by W. F. Hamilton, R. A. Woodbury and H. T. Harper Jr. (Arterial, Cerebrospinal and Venous Pressures in Man During Cough and Strain, Am. J. Physiol. **141**:42, 1944)[7] and by H. D. Laussen, R. A. Bloomfield and A. Cournand (The Influence of Respiration on the Circulation of Man, Am. J. Med. **1**:315, 1946) were up to approximately 140 mm. We recorded a pressure of 125 mm. for 1 patient with advanced cystic disease of the lungs (but no symptoms); the highest pressure in these control studies was 150 mm., in a patient with chronic granulomatosis of the lungs associated with exposure to beryllium compounds. A further check of the pressure recording for the patient with tussive syncope was the diastolic pressure of 70 mm. in the right ventricle, which was observed while he blew against a column of mercury with an air pressure of 70 mm.

were sustained long enough to demonstrate a pronounced reduction in the systemic arterial pressure to 60 systolic and 50 diastolic. After the paroxysm of coughing, the net pulse pressure in the right ventricle recovered more rapidly than the systemic

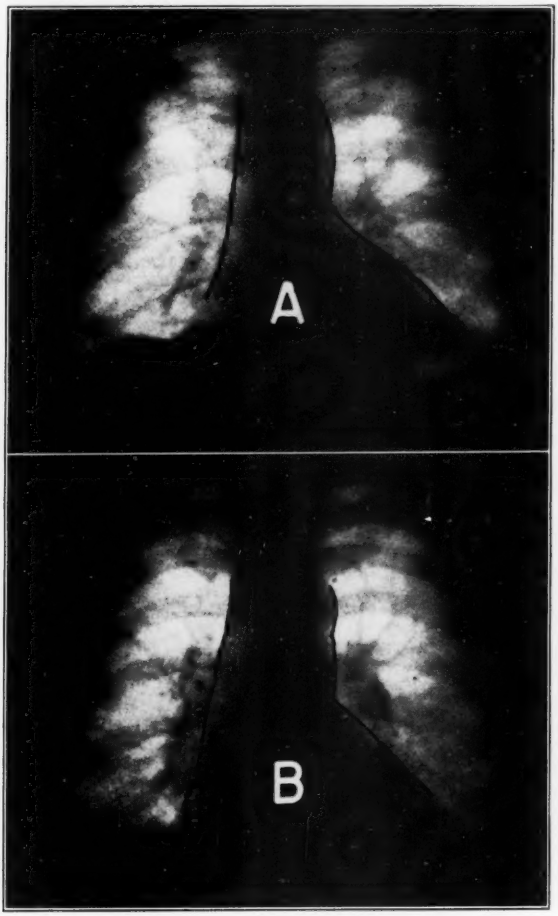

Fig. 2.—Selected enlargements from a cinefluorogram of the chest in case 1. *A*, expansion of the superior mediastinum, the right atrium, the pulmonary conus and the hilar shadows during quiet breathing; *B*, during coughing.

pulse pressure. Even with mild coughing the patient usually experienced transient lightheadedness and confusion; concomitantly the arterial oxygen tension was reduced by 20 mm. and the oxygen saturation by 6 per cent.

In order to ascertain whether the registered pressures in the right ventricle during coughing were entirely due to increased intrathoracic air pressure or were in part due to spasm of the pulmonary artery, the following observations were made: Cardiac catheterization was repeated, and a bronchoscope was placed in the trachea.[9] No laryngeal or bronchial obstruction was seen. Under these circumstances the patient was entirely unable to perform the Valsalva maneuver. He was

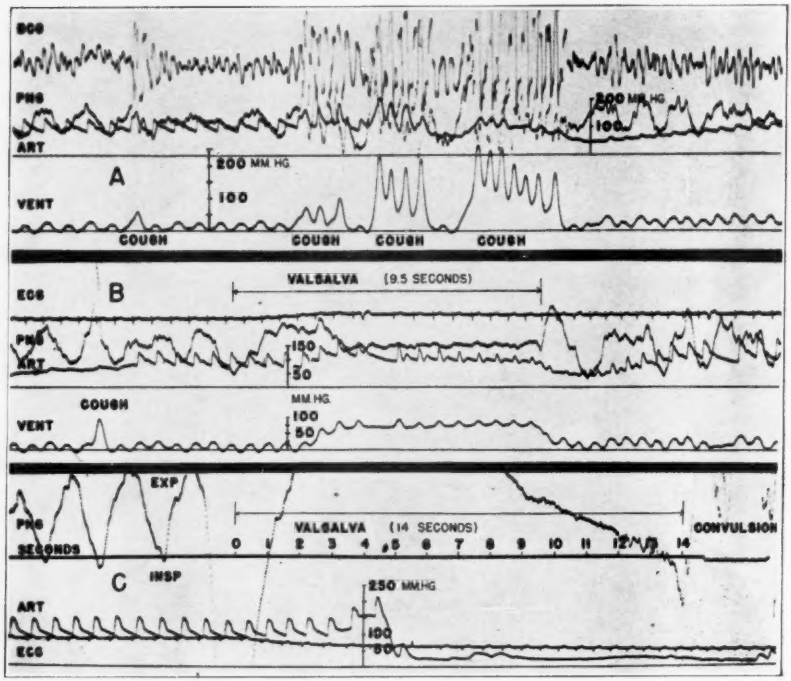

Fig. 3.—Hemodynamic records in case 1. *A*, the ballistocardiogram (BCG), the pneumogram of the chest (PNG), the intra-arterial pressure from the radial artery (ART) and the pressure in the right ventricle (VENT) during several paroxysms of coughing. During the last paroxysm pressures of 250 mm. were recorded; following the coughing, the arterial pressure dropped to 50 mm. and returned only slowly; during those few seconds the patient felt dizzy and confused. *B*, changes during a Valsalva experiment of short duration. The pulse pressure in both the radial artery and the right ventricle decreased toward the end of the effort. *C*, record of pressures in the femoral artery during a Valsalva experiment of longer duration. The return of the tracing in the pneumogram to the base line during the prolonged forced expiration was an artefact. Following a transient rise there was a sharp drop in arterial pressure to 50 mm. in the interval of 1 heart beat. Thereafter, there were no effective pulse beats until shortly after a convulsion had occurred, despite a normal sinus rhythm as shown in the electrocardiogram.

9. The bronchoscopic examination was made by Dr. E. B. Emerson Jr.

able to cough with considerable expulsive force, and the pressure in the right ventricle rose as high as 250 mm. (table 2). The endotracheal air pressure after removal of the bronchoscope was as high as 200 mm. with coughing. It should be noted, too, that although the patient was able to maintain the Valsalva experiment for as long as thirty-four seconds he did not lose consciousness.

Later Studies.—Two months later, the patient returned for further studies and stated that he had been coughing less and had had no further syncopal attacks. Whereas he had formerly shown borderline hypertension in the pulmonary circulation, especially with leg exercises, he then exhibited normal pressures in the

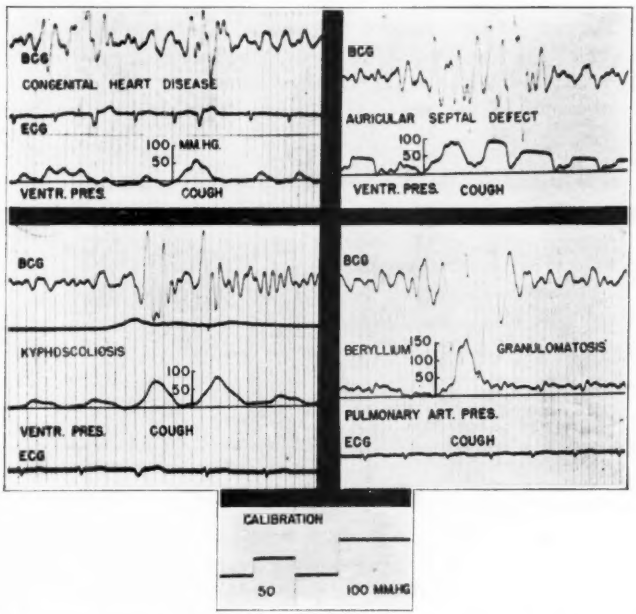

Fig. 4.—Intracardiac pressures during coughing in 4 patients studied for other conditions. Note the lack of overshooting in the calibration records.

right ventricle and the pulmonary artery, as determined by a third cardiac catheterization (table 2). The diastolic pressure in the right ventricle rose to 78 mm. on performance of the Valsalva maneuver (held for thirty-seven seconds) and to 255 mm. with coughing, but in neither instance was there any loss of consciousness. The vasodilating effects of amyl nitrite, tetraethylammonium chloride (3.5 cc. intravenously, 5 mg. per kilogram of body weight) and aminophylline were investigated. The first two medicaments caused the sensation of peripheral tingling, but no other effects. After only 0.09 Gm. of aminophylline U. S. P. had been given intravenously over two to three minutes' time, the patient experienced pain in the

left side of the chest, which was aggravated by deep breathing. This persisted for about half an hour and was unassociated with any changes in the heart rate, the blood pressure or the oxygen consumption or in the electrocardiogram or ballistocardiogram. Following oxygen therapy by mask the pain promptly disappeared. The pressure in the right ventricle during coughing was only 116 mm., but it seemed that the lower pressure on this occasion was due to the lessened vigor of coughing because of the pain in the chest rather than to a specific vasodilating effect of aminophylline on the pulmonary arterial tree. It could, of course, have been an expression of both factors. After these observations were made, oxygen was administered by mask and the pain promptly disappeared.

The patient experienced repeated episodes of syncope associated with coughing. He presented the features of abdominal obesity and mild pulmonary insufficiency. The Valsalva maneuver abruptly altered the hemodynamics of the pulmonary circulation by virtue of the increased

TABLE 2.—*Pressures* in Case 1*

	Resting	Coughing	Valsalva Experiment	Duration of Valsalva Experiment, Seconds
Maximal pressures during second catheterization				
Location				
Trachea	..	200	109	..
Right ventricle	41	260	75	28
Right ventricle (bronchoscope in trachea)	22	260	22	..
Effects of drugs on pressure in right ventricle				
Drug				
None	17	255	78	27
Amyl nitrite U. S. P.	22	...	..	..
Tetraethylammonium chloride	17	172	55	..
Aminophylline U. S. P.	17	116	50	..

* Mm. of mercury.

intrathoracic pressure (as postulated by Wilkins and Friedland[4]), which resulted in impaired cardiac output and in cerebral anoxia. On some occasions this procedure precipitated a convulsive seizure. Extraordinarily high pressures in the right ventricle, together with fluoroscopic evidence of the trapping of blood within the pulmonary circulation, were also observed during paroxysms of coughing. The mechanism of these changes in pressure was believed to be identical with that of the Valsalva maneuver. The pressure in the right ventricle during coughing and during the Valsalva maneuver was lower following the intravenous administration of either tetraethylammonium chloride or aminophylline. The untoward response of substernal pain to the latter drug made the interpretation difficult. There were no objective changes in the cardiac mechanisms during this painful episode, but the administration of oxygen relieved the symptomatic distress. Bronchoscopic intubation of the trachea failed to prevent the high pressures which occurred in the right

ventricle with coughing. Hence, this patient could produce not only high intrathoracic air pressures but also equally high, or higher, vascular pressures proximal to the pulmonary artery. Consequently, the possibility of spasm of the pulmonary artery could not be overlooked.

CASE 2.—J. S., a 49 year old metal sorter, had had a chronic cough for the past few years. During the previous fourteen months, he had experienced several

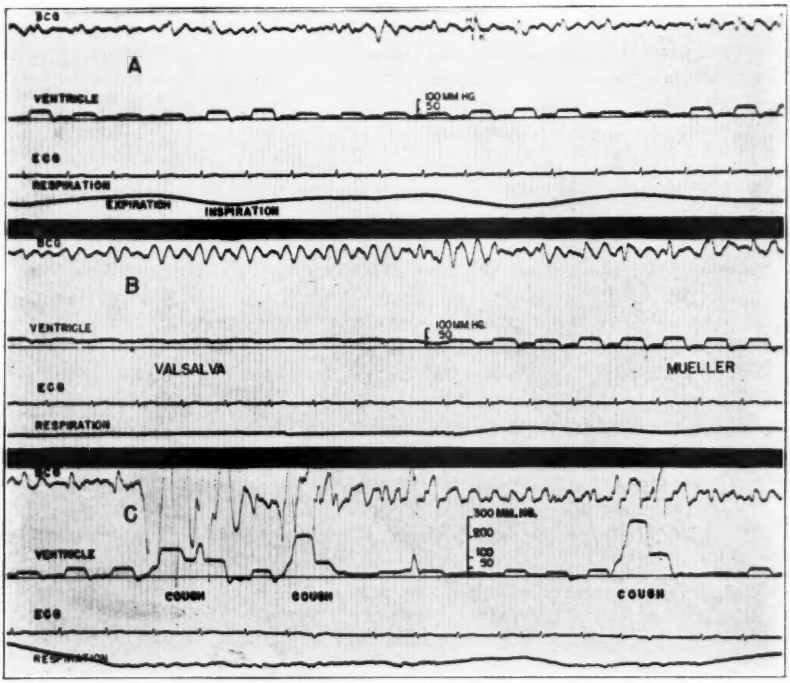

Fig. 5.—Intracardiac pressures in case 2. *A*, marked respiratory variations in pressure in the right ventricle. Note that the ballistocardiogram (BCG) also varied with respiration and that the configuration became normal only in inspiration. *B*, partial record of the end of a Valsalva experiment and the beginning of a Müller test. The pulse pressure in the right ventricle almost disappeared during the Valsalva experiment. *C*, the high pressures in the right ventricle during coughing (up to 270 mm.).

syncopal attacks occurring after severe bouts of coughing, usually following meals. Despite the fact that each time he had fallen backward, he had suffered no serious injury. His only other complaint was slight exertional dyspnea. He smoked about one and a half packs of cigarets daily.

Physical Examination.—The patient was a short, plethoric man with abdominal obesity. The anteroposterior diameter of the chest was somewhat increased, with slightly less expansion of the chest on the left side. Auscultation of the heart and lungs was noncontributory.

Laboratory Examination.—Fluoroscopic examination of the chest was unremarkable except for slight prominence of the pulmonary conus. Determination of the lung volumes revealed a moderate amount of emphysema with an increase of the residual air to 46 per cent of the total capacity. The venous pressure was elevated to 15 cm. of water and increased 0.5 cm. with pressure over the liver.

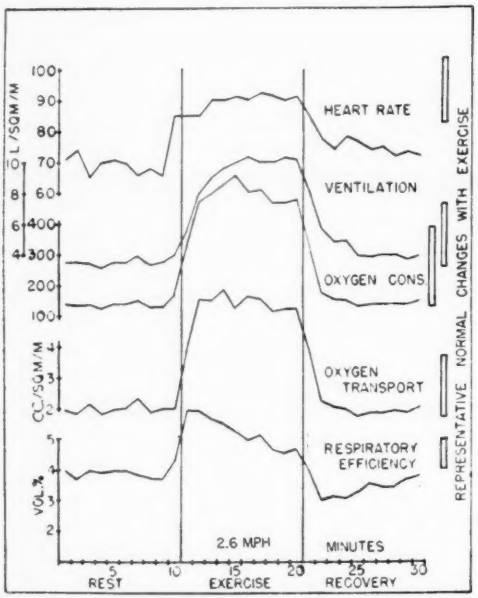

Fig. 6.—Exercise tolerance test in case 2, showing a comparatively normal performance.

Circulation times (determined with ether and macasol [10]) were within normal limits. The electrocardiogram was normal, but the ballistocardiogram showed an abnormal pattern (fig. 5 *A*). An exercise tolerance test on a motor-driven treadmill at 2.6 miles per hour for ten minutes showed no gross abnormality, but the patient experienced moderate dyspnea (fig. 6).

Cardiac catheterization was performed; pressures up to 270 mm. in the right ventricle were recorded with mild coughing (fig. 5 *C*). There was no symptomatic

10. Each 2 cc. ampul of macasol contains the following: magnesium sulfate, 0.680 Gm.; magnesium gluconate, 0.324 Gm.; calcium sulfate, 3.2 mg., and copper sulfate (as preservative), 0.02 mg.

distress, but the patient was reluctant to cough hard or long because of painful symptoms from a previously repaired inguinal hernia on the right side. During quiet breathing the pressure in the right ventricle in systole varied from 18 systolic and 0 diastolic to 41 systolic and 5 diastolic at the peak of expiration and inspiration, respectively (fig. 5*A*). The pulse pattern and the net pressure in the right ventricle during the Valsalva maneuver were greatly reduced (fig. 5*B*). The arterial blood was 93.6 per cent saturated, with an oxygen tension of 59 mm.

Despite the failure to demonstrate syncope following cough, the body build, the exaggerated respiratory variation of pressures in the right ventricle, the increased residual air and the acute elevation of pressure in the right ventricle to 270 mm. with coughing were all features compatible with this syndrome. It was felt that observations during an acute paroxysm of coughing might confirm the diagnosis, as in the first case.

COMMENT

Abnormally high pressures in the right ventricle during coughing were obtained in both patients studied. In the first case it was fairly well established that the syncope and convulsions resulting from paroxysms of coughing or from the Valsalva maneuver were caused by congestion of the cerebral veins, decreased cardiac output and anoxemia. The second patient, though not exhibiting syncope or convulsions while under observation, presented clinical and laboratory evidence similar to the first patient, and it is assumed that syncope would have occurred had he been able to sustain either the cough or the Valsalva maneuver. Studies of the first patient to elucidate the mechanism of the pressures in the right ventricle with coughing were inconclusive. The possibility of reflex spasm of the pulmonary artery existed in view of the fact that the same high pressures in the right ventricle with coughing were produced with a bronchoscope in the trachea.

The importance of nicotine inhaled from smoking tobacco in these reactions deserves a comment. The initial application of nicotine to the sympathetic ganglions supplying the lungs of experimental animals (dogs) causes vasoconstriction, and the late effect is that of paralysis of the ganglions.[11] Whether or not the excessive smoking of cigarets could permit the absorption of nicotine in sufficient quantity to cause pulmonary vasoconstriction cannot be answered at the time of writing.

From these considerations it seems that the term "tussive syncope" is more appropriate for this syndrome than "laryngeal epilepsy," since the syncopal response is dependent on circulatory disturbances due to coughing and is not due to epilepsy.

11. Daly, I. de B.; Duke, H.; Heff, C. O., and Weatherall, J.: Pulmonary Vasomotor Fibers in the Sympathetic Chain and Its Associated Ganglia in the Dog, Quart. J. Exper. Physiol. **34**:285, 1948.

SUMMARY

The background of Charcot's syndrome of laryngeal epilepsy is briefly reviewed, and the laboratory findings in 2 similar cases are described. Both the Valsalva maneuver and paroxysmal coughing were found to impede venous return and pulmonary circulation and to decrease cardiac output, confirming the findings of Wilkins and Friedland.[4] Cerebral congestion alone was not sufficient to cause syncope, but cerebral congestion occurred in addition to anoxemia and cerebral anoxia. In the first patient, syncope and even convulsions were produced by the Valsalva maneuver while he was in the recumbent position. The possibility that spasm of the pulmonary artery occurred, in addition to a pronounced increase in intrathoracic air pressure, was investigated with inconclusive results. The term "tussive syncope" is believed to be more appropriate than "laryngeal epilepsy."

AUREOMYCIN TREATMENT OF PNEUMOCOCCIC PNEUMONIA

Clinical and Laboratory Studies on Thirty-Three Patients

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BOSTON

AUREOMYCIN is an antibiotic which, from the results of early studies in vitro and in experimental infections, as well as in initial clinical trials, appears to have a wider range of activity than its successful antecedents, penicillin and streptomycin.[1] This range encompasses most of the known causative agents of the acute pneumonias, including the gram-positive and gram-negative bacteria, the organisms of the psittacosis–lymphogranuloma venereum group and the Q fever and other rickettsias. Since aureomycin was also found to be effective when given by mouth and was essentially free of serious toxic effects, it seemed particularly suitable for extended clinical trials in cases of pneumonias of diverse origin.

During the past year an attempt was therefore made to evaluate the therapeutic effectiveness of aureomycin in the various types of pneumonia and in some of the other severe acute infections of the respiratory tract that were available for study. The present paper deals with the results of the clinical and laboratory studies made on 33 consecutive

Aided by a grant from the United States Public Health Service.

The aureomycin was provided by the Lederle Laboratories, Division of American Cyanamid Company, Pearl River, N. Y.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

1. Duggar, B. M., and others: Aureomycin: A New Antibiotic, Ann. New York Acad. Sc. **51:** 175-342 (Nov. 30) 1948.

patients with pneumococcic pneumonia who were treated with this agent. The findings in various other groups of cases are presented in separate communications.[2]

MATERIALS AND METHODS

Selection of Cases.—The 33 patients included in this study were all admitted to the adult medical wards of the Boston City Hospital before June 15, 1949. Before any aureomycin was given these patients satisfied all the following criteria: 1. In each case the history and findings by physical examination were consistent with a diagnosis of pneumococcic pneumonia. Roentgenograms of the lungs were usually taken at the time of admission to the hospital, but occasionally they were taken a day or two later; these also showed lesions consistent with pneumococcic pneumonia in each instance. 2. All patients were acutely ill and febrile at the time the first dose of aureomycin was given. 3. No previous treatment with antiserums, sulfonamides or antibiotics had been given. 4. Blood and sputum were obtained for cultures, and pneumococci of specific types were isolated and identified from one or both of these sources. All patients with pneumococcic pneumonia who satisfied these criteria have been included, and, in fact, no patient with pneumococcic pneumonia who was treated with aureomycin has been omitted.

Clinical Studies.—Each patient was observed closely and examined before and at frequent intervals after administration of aureomycin was started until they were well along in convalescence and the common laboratory tests were carried out as indicated. Roentgenograms of the lungs, in addition to those made on admission were repeated as often as feasible, usually twice a week during the hospital stay.

Bacteriologic Studies.—Blood cultures were made before treatment was started in every case and were repeated during the next few days when indicated. Fresh sputum specimens were collected before use of aureomycin was started and at frequent intervals thereafter. The patient was required to rinse the mouth and throat thoroughly with water and then to drink a few ounces of tap water. The sputum that was then raised after vigorous coughing was collected in a sterile Petri dish and taken directly to the laboratory. It was then emulsified, streaked on the surface of blood agar plates, planted in blood broth and in many cases also inoculated intraperitoneally into mice. Smears were made and examined in Gram-stained preparations as well as in the fresh state by the Neufeld method. The latter preparations were used not only to identify the types of pneumococci (Diplococcus pneumoniae) but also to estimate the numbers of the specific types of pneumococci that were present in the sputum by counting the organisms showing the characteristic capsular swelling in a large number of consecutive oil immersion fields. The blood broth cultures, characteristic colonies from the blood agar plates and the peritoneal exudate and heart's blood cultures of mice were each examined for specific pneumococcus types by the Neufeld method.

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2. (*a*) Collins, H. S.; Gocke, T. M., and Finland, M.: Aureomycin Therapy of Nonpneumonic and Nontuberculous Bacterial Infections, Arch. Int. Med., this issue, p. 875. (*b*) Finland, M.; Wells, E. B.; Collins, H. S., and Gocke, T. M.: Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections, With and Without Pneumonia, Am. J. Med., to be published. (*c*) Collins, H. S.; Wells, E. B.; Gocke, T. M., and Finland, M.: Treatment of Primary Atypical Pneumonia with Aureomycin, Am. J. Med., to be published.

Tests for Sensitivity to Aureomycin.—The various specific types of pneumococci as well as some of the other organisms which grew in abundance in the cultures of the sputum were isolated in pure culture and tested for sensitivity to aureomycin. A serial dilution method in broth or on the surface of aureomycin-containing blood agar plates was used for these tests.[3] The aureomycin hydrochloride solutions used for these tests were freshly prepared from the crystalline state each time.

Most of these studies were carried out by Clare Wilcox and Janice M. Bryan. The pneumococcus-typing serums and the aureomycin hydrochloride in sterile vials were provided by the Lederle Laboratories.

Serologic Tests.—Blood for the serologic tests was also obtained before and at suitable intervals after the aureomycin treatment was started. The serums were removed after warming the blood to 37 C., and they were then stored in rubber-stoppered pyrex® tubes at 5 C. The acute and convalescent phase serums were always tested simultaneously. The following tests were carried out with the serums of most of the patients: tests for cold agglutinins and for Streptococcus MG agglutinins; inhibition of chicken cell agglutination with influenza A (PR8) and B (Lee) viruses and tests for agglutinins for the homologous and for some heterologous types of pneumococci. The methods employed in most of these tests are given elsewhere.[2e] The antigens used for the pneumococcus agglutinations were saline suspensions of formaldehyde-killed fully grown pneumococcus cultures, some of which were stock preparations that had been kept in a refrigerator for several years and others were freshly prepared from strains isolated from patients in this study. All these tests were carried out by Mildred W. Barnes. The serums of a few of these patients were also tested for complement-fixing antibodies for psittacosis and Q fever, either in the Department of Virus and Rickettsial Diseases of the Army Medical Center, through the courtesy of Dr. Joseph E. Smadel, or in the Division of Viral and Rickettsial Research of the Lederle Laboratories, through the kindness of Dr. Herald R. Cox.

ANALYSIS OF THE CASES STUDIED

Sex and Age (table 1).—There was the usual predominance of males over females. The patients ranged in age from 13 to 75 years, with a preponderance in the older age groups, and 8 of the 33 patients, including 4 with bacteremia, were 65 years of age or older.

Pneumococcus Types.—The distribution of the types of pneumococci that were identified is also shown in table 1. Sixteen different types of pneumococci were represented and two thirds of the cases were due to types 1 to 8, exclusive of type 6. It is significant that in 6 of the remaining 11 patients, that is, in the ones having pneumococci of the so-called higher types, the same type was obtained from both blood and sputum. A second type of pneumococcus was identified in the sputum of 2 patients in addition to type 2 pneumococci: type 7 in 1 and type 24 in the other.

Underlying Complications.—Some significant underlying complication was present in 18 of the 33 patients, as shown in the lower portion of table 1. Six of the patients had acute alcoholic intoxication when admitted to the hospital; in 3 of these patients delirium tremens

3. Paine, T. F., Jr.; Collins, H. S., and Finland, M.: Bacteriologic Studies on Aureomycin, J. Bact. **56:** 489-497 (Oct.) 1948.

developed, either before or shortly after treatment with aureomycin was started, and 1 of the latter also had severe cirrhosis of the liver. Evidence of chronic bronchitis and bronchiectasis was made out from the history and the physical and roentgenographic findings in 2 patients, and the patient with bronchial asthma had persistent symptoms during the acute state of the pneumonia and to a milder degree throughout the period of hospitalization.[4] The patient with rheumatic heart disease had signs of moderate pulmonary congestion and edema on admission to

TABLE 1.—*Distribution of Patients by Sex, Age and Pneumococcus Type*

	Number of Patients *
Sex	
Male	20
Female	13
Age	
Under 20 years	4 (2)
20-39 years	9 (2)
40-59 years	12 (3)
60 years and older	8 (4)
Type	
1	6 (3)
2	5 †
3	3
4	2 (1)
5	2
7	3 (1)
12	2 (2)
14	2 (1)
11, 18, 40 (1 each)	3 (3)
8, 19, 20, 31, 33 (1 each)	5
Complicating conditions	
Acute alcoholism	3
Alcoholism and delirium tremens	3
Chronic bronchitis and bronchiectasis	2
Bronchial asthma	1
Cardiac failure (rheumatic)	1
Severe malnutrition	2
Addiction to diacetylmorphine (heroin)	1
Jaundice	2
Agranulocytosis and diabetic acidosis	1
Old cerebral injury	1
Pyelonephritis (K. pneumoniae)	1

* The number of those with positive blood cultures is indicated in parentheses.
† One had type 7 and another had type 24 pneumococci in the sputums in addition. (These are not listed in the table.)

the hospital and was promptly digitalized. The jaundice noted in 2 patients was mild (icterus index 12.5 to 20.0) and probably was related to the pneumonia, since it cleared promptly after treatment was started. The patient with agranulocytosis and diabetic acidosis and the one with the old cerebral injury both died, and they will be considered separately later.

Aureomycin Sensitivity of Pneumococcus Strains (table 2).—The sensitivity of the pneumococci obtained from the blood and sputum was

4. This patient, N. G., also had eosinophilia of the blood and sputum; details of this case are presented elsewhere.[2e]

tested in 30 of the patients. All the strains of the same type of pneumococcus obtained from the blood and sputum before treatment and from subsequent sputum samples when pneumococci could still be isolated had the same sensitivity to aureomycin. The sensitivity of the 32 different strains tested ranged from 0.39 to 3.12 micrograms per cubic centimeter, the majority being completely inhibited by less than 1 microgram per cubic centimeter. A comparison of the sensitivity of these strains with the strain Streptococcus 98, which was included as a control in every test, is also shown in table 2. All but 5 of the 32 strains of pneumococci were at least as sensitive as Streptococcus 98, and 11 were two or four times as sensitive.

TABLE 2.—*Aureomycin Sensitivity of 32 Strains of Pneumococci from 30 Patients*

Sensitivity Mcgm./Cc.*	Number of Strains
0.39	7
0.78	13
1.56	7
3.12	5
Comparison with Str. 98 (Control) †	
Four times as sensitive	5
Twice as sensitive	6
Same sensitivity	16
Half as sensitive	4
One fourth as sensitive	1

* Complete inhibition (no growth on subculture) in eighteen hours.
† Sensitivity of Streptococcus 98 was 0.78 or 1.56 micrograms per cubic centimeter in different tests.

STATUS OF THE DISEASE AT THE START OF AUREOMYCIN TREATMENT

An analysis of some of the relevant features of the disease in the 33 patients at the time aureomycin treatment was begun is given in table 3. As already noted, none of these patients had previously received any serotherapy, sulfonamides or antibiotics. The first dose of aureomycin was given in most instances on or before the fifth day of illness, and all the patients were acutely ill at the time. Pneumococcemia was demonstrated in the pretreatment blood cultures in one third of the patients. The pulmonary lesion, as judged by physical and roentgenographic indications, was limited to a single lobe in most of the patients; two or three lobes were involved in 9 patients, and in only 4 of the latter was the lesion bilateral.

All the patients were febrile when aureomycin treatment was started, and the temperature at that time was below 101 F. in only 1 of them. In the majority, the temperature was 103 F. or higher, and in 3 patients

it was over 105 F. The leukocyte counts ranged from 2,200 to 33,700 per cubic millimeter, with totals below 10,000 in 4 and over 25,000 in 6. An attempt was also made to arrive at a general estimate of the severity of the illness in each patient from all the observations made at the time aureomycin therapy was undertaken. Most of the patients were considered to be moderately or severely ill. In only 2 patients was the illness judged to be mild, and 1 patient was almost moribund at the time.

TABLE 3.—*Status of 33 Patients with Pneumococcic Pneumonia at the Start of Aureomycin Treatment*

Findings	Number of Patients
Day of disease	
1	4
2	3
3	6
4	11
5	4
6-14	5
Blood culture	
Positive	11
Negative	22
Pulmonary involvement	
1 lobe	24
2 lobes (unilateral)	5
2 or 3 lobes (bilateral)	4
Temperature F.	
100.4-101.9	5
102.0-102.9	9
103.0-103.9	9
104.0 or higher	10
Leukocyte count	
Less than 10,000	4
10,000-14,900	11
15,000-19,000	8
20,000-24,000	4
25,000 or more	6
Estimated clinical severity	
Mild	2
Moderate	18
Severe	12
Critical	1

DOSAGE

An analysis of the dosage of aureomycin used for the 33 patients with pneumococcic pneumonia is given in table 4. Most of the patients received all the aureomycin by mouth in doses varying from 1.0 Gm. every four or six hours to 0.5 Gm. given at intervals of four, six or eight hours. In 9 of the 16 patients who received individual doses of 1.0 Gm., these were reduced to 0.5 Gm. after the temperature reached normal and the condition had improved.

The total oral dose of aureomycin ranged from 5.5 to 46.5 Gm. given over a period ranging from two to fifteen days. Most of the patients received less than 20 Gm. and were treated for five days or less. The

average dose for the 27 patients who were treated orally was 17.7 Gm. given over an average of about five and one-half days.

Parenteral therapy was used in the treatment of 6 patients. Two of these patients received repeated doses of 100 mg. each, some given intravenously and the rest intramuscularly at intervals of two to four hours. In these cases, each dose was given in 10 cc. of 0.7 per cent sodium carbonate solution, and the intravenous doses were given very slowly, ten to fifteen minutes being taken for each injection. Both of these patients died, one after receiving only five doses in fourteen hours and the other after six doses had been given in fourteen hours.

TABLE 4.—*Analysis of Dosage*

	Number of Patients
Dosage started by mouth	
1.0 Gm. every 4 hours	8
1.0 Gm. every 6 hours	8
0.5 Gm. every 4 hours	5
0.5 Gm. every 6 hours	4
0.5 Gm. every 8 hours	2*
Total oral dose	
Less than 10 Gm.	4
10 to 19 Gm.	14
20 to 29 Gm.	6
30 Gm. or more	3
Average (27 patients): 17.7 Gm.	
Total duration of oral therapy	
2 or 3 days	4
4 or 5 days	13
6 or 7 days	5
8 days or longer	5
Average (27 patients): 5.6 days	
Parenteral therapy only	
Intravenous and intramuscular	
100 mg. every 2 to 4 hours	2
Average total dose: 550 mg.	
Intravenous only	
500 mg. once daily †	4
Average total dose: 2.05 Gm.	

* One of these patients received several doses of 100 mg. intramuscularly every four hours before the first oral dose.

† One patient received an initial dose of 750 mg.; in another patient oral aureomycin was given during convalescence for underlying chronic bronchopulmonary infection.

Four other patients received aureomycin for their pneumonia only by the intravenous route. The individual doses for these 4 patients consisted of 500 mg. of crystalline aureomycin hydrochloride given in 1.0 or 1.5 liters of either istonic sodium chloride solution or 5 per cent dextrose solution in distilled water. These were given once daily by slow drip, taking about an hour or longer for each injection. The initial dose for 1 patient was 750 mg. given in the same manner. No special buffers were used with these injections, and the reaction of the final solutions was about p_H 3.5 to 4.0. The average total dose for these 4 patients was 2.05 Gm., and the interval between the first and the last dose averaged seventy-two hours.

Two of the patients received penicillin in addition to aureomycin; one of them was the patient with agranulocytosis who died, and the other received the penicillin only during convalescence. No other antimicrobial agents were used for any of the remaining patients.

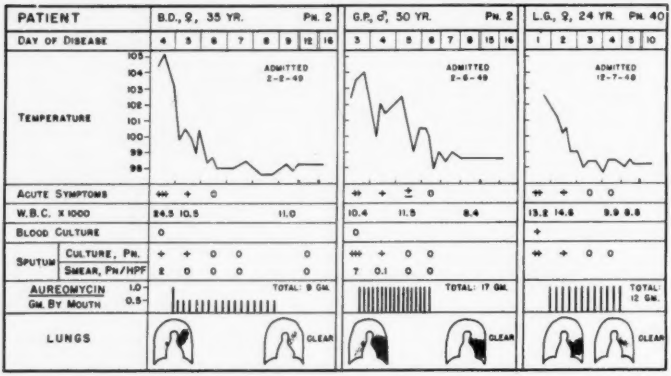

Chart 1.—Significant data an 3 patients with pneumococic pneumonia who were treated with aureomycin by mouth.

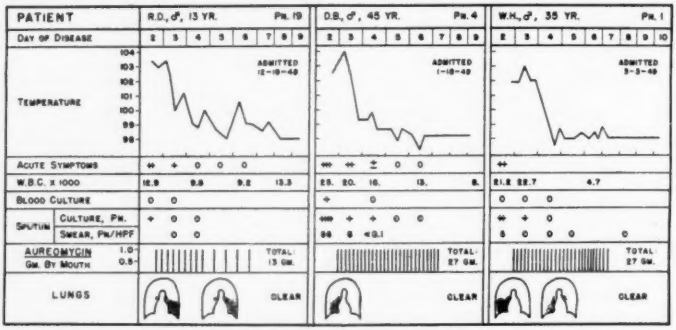

Chart 2.—Course and other significant data in cases of 3 additional patients with pneumococcic pneumonia treated with aureomycin by mouth.

RESULTS OF AUREOMYCIN THERAPY

The general effects of aureomycin by mouth on the clinical course and bacteriologic observations in the first 4 patients of this series have been noted briefly in a preliminary communication.[5] These effects as

5. Collins, H. S.; Paine, T. F., Jr., and Finland, M.: Aureomycin in Treatment of Pneumococcal Pneumonia and Meningococcemia, Proc. Soc. Exper. Biol. & Med. **69:** 263-265 (Nov.) 1948.

observed in 6 other cases of moderate severity are illustrated graphically in charts 1 and 2. The course and relevant data on 3 additional patients, who were each over 65 years old and bacteremic and, therefore, may be considered as having a very grave prognosis,[6] are shown in chart 3. Two patients died within eighteen hours of the time aureomycin treatment was started, and the salient features of these cases will be considered separately. An analysis of the effects of aureomycin on the clinical course of the 31 patients who recovered is presented in table 5. The 4 patients who were given the aureomycin by the intravenous route

TABLE 5.—*Effect of Aureomycin on the Clinical Course in 31 Patients with Pneumococcic Pneumonia*

	Number of Patients
A. First major sustained drop in temperature	
Less than 12 hours	10
12-23 hours	15
24-35 hours	3
36-47 hours	3
B. Total duration of temperature over 99.2 F.	
Less than 24 hours	12
24-47 hours	11
48-71 hours	3
72 hours or longer	5
C. Major sustained improvement in symptoms	
12 hours or less	12
13-24 hours	13
25-48 hours	6
D. Essentially complete symptomatic improvement	
Less than 24 hours	7
24-47 hours	16
3 or 4 days	5
More than 4 days	3
E. Definite clearing of pulmonary lesion as determined by physical examination or by roentgenograms	
2-4 days	13
5-6 days	9
7-8 days	6
9 or more days	3
F. Lungs entirely clear by physical examination, roentgenograms or both	
7 days or less	17
8-14 days	11
More than 14 days	3

are also included in this analysis: the data on 3 of these patients are shown in chart 4.

Effect on Fever.—There was a marked drop in temperature during the first two days after the administration of aureomycin was started in all 31 patients who recovered. In all but 6 of these patients the major reduction in the fever had occurred within the first twelve or twenty-four hours. There were only 8 patients in whom any fever persisted or recurred after the second day, and in these patients the temperature did not usually exceed 100 F. after that time. Three of these patients became afebrile during the third day, and in 2 others the temperature remained normal after the fourth day.

6. Tilghman, R. C., and Finland, M.: Clinical Significance of Bacteremia in Pneumococcic Pneumonia, Arch. Int. Med. **56**: 602-619 (April) 1937.

Of the 3 patients whose fever persisted for longer than four days, 1 had delirium tremens and in him a sterile pleural effusion also developed. The course of this patient, J. A., is shown in chart 5. In a second patient the fever was associated with a persistent leukocytosis, but the patient had no localizing signs or symptoms of any complication

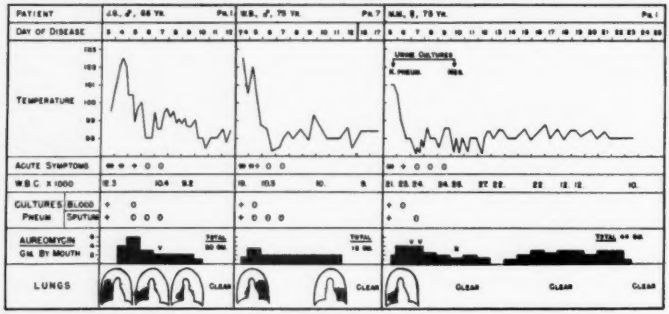

Chart 3.—Data on 3 bacteremic patients over 65 years of age with pneumococcic pneumonia treated with aureomycin by mouth.

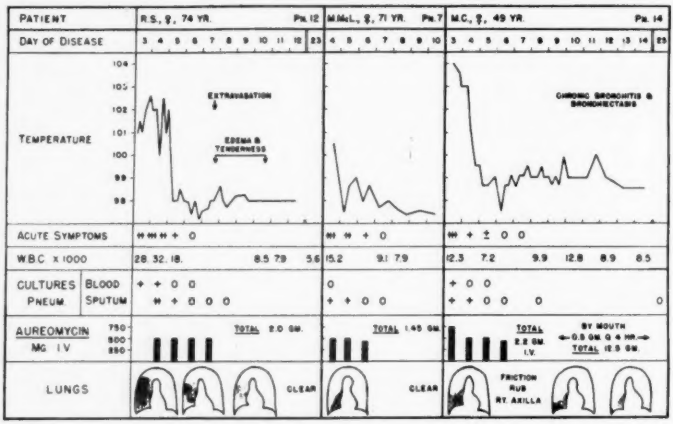

Chart 4.—Course and significant data in cases of 3 patients with pneumococcic pneumonia treated with aureomycin intravenously.

and the lesion in the lung was clearing rapidly during this time. The fever subsided while the aureomycin was still being given, and test doses of aureomycin subsequently failed to reproduce the fever; hence the fever cannot definitely be ascribed to the antibiotic. The data on this patient, M. McC., are shown in chart 6. In the third patient, the pneu-

monia began during a severe attack of influenza A, and treatment, which was started with intramuscular doses, resulted in a slow but steady defervescence of fever, which cleared only after oral therapy was given. The

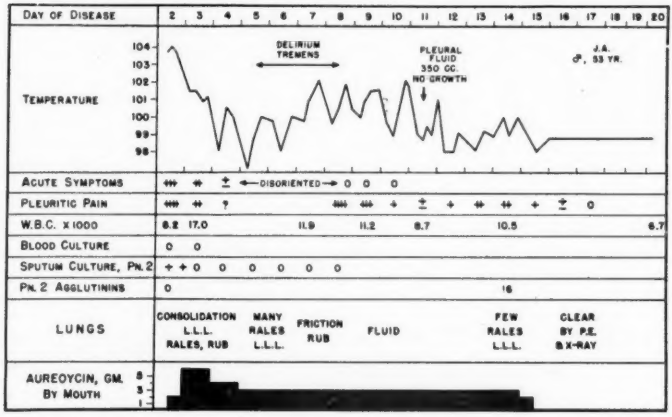

Chart 5.—Course and significant data in the case of a patient with type 2 pneumococcus pneumonia treated with aureomycin by mouth.

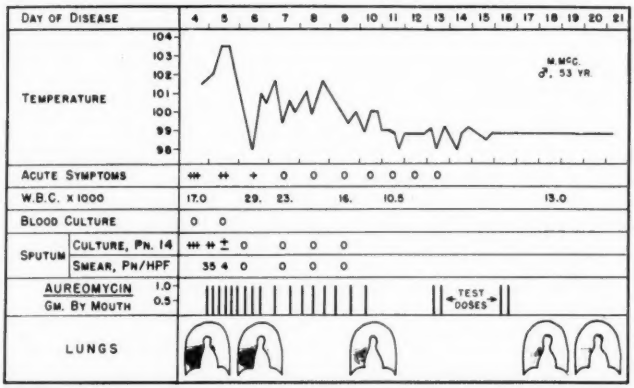

Chart 6.—Persistent fever and leukocytosis in the case of a patient with type 14 pneumococcus pneumonia treated with aureomycin by mouth.

course and findings in the case of this patient, G. G., have been presented elsewhere.[2c]

Effect on Symptoms.—Improvement in the acute symptoms of the pneumonia usually paralleled the drop in temperature. In some

patients the subjective improvement actually preceded by several hours the major drop in temperature, and only an occasional patient continued to appear acutely ill for any length of time after the temperature had dropped to a nearly normal level. There were 5 patients who continued to have minor symptoms during the third and fourth day after treatment was begun but only 3 continued to have significant symptoms of acute illness after the fourth day.

One of the latter was patient J. A. who had the pleural effusion. The second patient (M. C., chart 4) received intravenous therapy at first and showed marked improvement. There was some persistence of pleural pain, cough and expectoration, and roentgenograms suggested the presence of fluid, but the signs and symptoms cleared after oral administration of aureomycin was instituted. The third patient was the one who had bronchial asthma; she continued to have some respiratory distress and wheezing after her fever and other acute symptoms had subsided.

Effect on the Pulmonary Lesion.—The lungs, in general, cleared rapidly after aureomycin therapy was started, as indicated in sections E and F in table 5. Definite and usually marked clearing was evident from the physical signs and roentgen observations within six days after treatment was started in more than two thirds of the patients who recovered. Signs of consolidation or fluid persisted over most of the affected area for more than eight days in only 3 patients.

With the exception of these 3 patients, complete clearing was demonstrated in roentgenograms taken on or before the end of the second week after the aureomycin treatment was initiated. In several patients, moreover, the last roentgenogram which still showed pulmonary infiltrations to be present had been taken from four to eight days earlier, and in most of them the pulmonary lesions had already largely cleared at that time. The 3 patients whose lesions persisted longer than two weeks were also the ones whose symptoms persisted the longest.

EFFECT OF AUREOMYCIN ON THE BACTERIOLOGIC FLORA

Effect on Bacteremia.—Pneumococci were obtained from the pretreatment blood cultures in 11 patients, but only one of the blood cultures taken after treatment was started was positive. This culture was obtained nine hours after the first parenteral dose of aureomycin was given to the patient with agranulocytosis, and the next culture, taken three hours later, showed no growth.

Effect on the Pneumococci in the Sputum.—Attempts were made to identify and isolate pneumococci from the sputum in all of the patients before and at frequent intervals after aureomycin treatment was started. The results of the sputum studies are summarized in table 6. In 11

patients, including 4 with bacteremia, the only specimens of sputum which yielded pneumococci were those obtained before the first dose of aureomycin. The first specimen in which pneumococci could not be identified either in direct smears or by the various cultural methods was obtained eight to twelve hours after the first dose in 4 of these 11 patients, within the first twenty-four hours in 5 others and within thirty-six hours after treatment was begun in the remaining 2. There were only 2 patients in the entire series in whom pneumococci were still demonstrable in sputum more than thirty-six hours after treatment was started, the longest interval being fifty-nine hours. It is thus seen that not only the pneumococcemia was promptly cleared but the pneumococci were rapidly eliminated from the sputum after the aureomycin treatment was started.

TABLE 6.—*Effect of Aureomycin on the Persistence of Pneumococci in the Sputum*

Interval After Start of Aureomycin Therapy	Number of Patients *
A. Last sputum in which pneumococci were demonstrated	
Pretreatment only	11 (4)
Less than 12 hours	9†(2)
12-23 hours	8 (3)
24-35 hours	3 (1)
36-47 hours	1 (1)‡
48-59 hours	1
B. First sputum in which pneumococci could no longer be demonstrated	
Less than 12 hours	4 (1)
12-23 hours	10 (6)§
24-35 hours	9 (1)
36-47 hours	5 (1)
48-59 hours	3 (1)
60-86 hours	2 (1)

* Two of the patients are listed twice (once for each type of pneumococcus). The parentheses indicate the number with bacteremia.

† One of these patients died before further specimens were obtained.

‡ No further sputum was available in this patient.

§ One fatal case is included in this figure.

Most of the strains of pneumococci isolated from sputum during or after the aureomycin treatment were tested for sensitivity to the antibiotic simultaneously with the corresponding pretreatment strains that had been isolated from both sputum and blood of the same patients. All strains of the same type obtained from the same patient were found to have identical sensitivity to aureomycin.

Results of Intravenous Therapy.—In the 4 patients who were treated with daily intravenous injections, the effects on the acute disease and on the bacteriologic findings were quite similar to those observed in the patients who received larger and more frequent doses by mouth. The major drop in temperature and symptomatic improvement occurred in each of these patients before the second dose was given. The optimum dose by the intravenous route has not been determined. The course and

relevant data in the cases of 3 of these 4 patients, including the only one of the 4 who later received aureomycin orally, are shown in chart 4. The oral therapy was given to this patient after the acute symptoms had been entirely relieved, in an attempt to influence an underlying chronic bronchopulmonary infection and a suspected pleural effusion.

REPORT OF FATAL CASES

In both of the fatal cases, all the aureomycin was given parenterally and death occurred within eighteen hours after the first dose was given. The salient features of these 2 cases may be summarized briefly.

The first patient was a 53 year old white man, known to have diabetes of long standing, who had been taking insulin regularly. The only history pertaining to the immediate illness that was obtainable at the time of admission was that the patient had been vomiting and coughing for three days, complained of bilateral pleuritic pain and was raising brownish sputum for two days. On the day before entry he was unable to work and a physician found his temperature to be 103 F. When first seen, he appeared extremely ill, semistuporous, markedly dehydrated, dyspneic and cyanotic. His temperature was 104 F., pulse rate 150, respiration rate 45 and blood pressure 70 systolic and 50 diastolic. Consolidation of the lower two thirds of the right lung was made out by physical examination and verified by roentgenograms. The blood sugar was 318 mg. per hundred cubic centimeters; carbon dioxide content 34 volumes per cent and serum chlorides 91 milliequivalents per liter, and the urine gave a positive reaction for sugar and showed a trace of acetone. The white blood cell count was 2,200, of which 55 per cent were polymorphonuclears, all of them "extremely toxic."

Aureomycin was given in 100 mg. doses parenterally, each in 10 cc. of dilute sodium carbonate buffer at about three hour intervals; a total of five doses were given, three of them intravenously and the third and the last doses intramuscularly, all without any untoward effects. At the time of the last two doses, the patient was also given penicillin, 200,000 units intravenously with one and 500,000 units intramuscularly with the other. He was also treated vigorously for his diabetes with insulin and parenteral fluids. A second leukocyte count, made a few hours after entry, showed 1,200 cells, and the smear showed no granulocytes. There was no improvement in the patient's general condition, and he died about eighteen hours after the first dose of aureomycin.

Blood cultures taken on admission and again before the first and third doses of aureomycin all showed type 11 pneumococci. A fourth culture of the blood taken before the first dose of penicillin showed no growth, and culture of the cardiac blood taken at autopsy showed only Aerobacter aerogenes and no pneumococci. Sputum was not obtainable, and pharyngeal cultures made before treatment showed type 11 pneumococci in abundance and a few colonies of Staphylococcus aureus. A second throat culture, made ten hours later, showed only two colonies of type 11 pneumococci, a few colonies of Staph. aureus and of Hemophilus influenzae and a single colony of A. aerogenes. Each of the cultures made of materials aspirated from all parts of the lung at the time of death, and those made from all lobes of the lungs at autopsy yielded a heavy growth of A. aerogenes in almost pure culture. No pneumococci could be identified, either directly by the Neufeld reaction or in the cultures from any of the autopsy materials. The strains of A. aerogenes from the various cultures were all completely inhibited

by aureomycin in concentration of 12.5 micrograms per cubic centimeter, the staphylococci and H. influenzae were both inhibited by 3.12 micrograms per cubic centimeter and the pneumococci were all sensitive to 0.78 micrograms per cubic centimeter.

In the second patient, a 21 year old Negro, the acute illness, which was preceded by mild coryza and cough, began with a shaking chill two days prior to admission to the hospital. This was followed by fever, an increase in cough, which became productive of blood-tinged sputum, and pleuritic pain, which was localized in the left upper anterior part of the chest. The only significant history of other illness was that of a head injury eight years previously after which he was unconscious for some time and then was left with a hemianopsia lasting two months. Since that time he had had several recurrences of hemianopsia, each lasting a few days and induced by jarring of the head. He was acutely but not critically ill and had signs of consolidation limited to the lower lobe of the left lung. The temperature was 104.5 F., pulse rate 112, respiration rate 40 and blood pressure 100 systolic and 64 diastolic. The white blood cell count was 9,100, of which 92 per cent were polymorphonuclears, most of them young forms. Pneumococcus type 1 was identified directly in the sputum, and the blood culture showed no growth.

Aureomycin was given in 100 mg. doses as in the previous case, beginning with one intravenous and one intramuscular injection and followed at two to four hour intervals by three intramuscular injections and a final one given intravenously because of the local soreness at the sites of the previous injections. There were no other untoward effects noted, and the patient appeared to improve rapidly. After the last injection the patient was cheerful, did not appear "toxic," ate his evening meal and enjoyed a visit from his friends. He was later found dead in bed, without evidence of antecedent activity, three hours after the last dose and seventeen hours after the first dose of aureomycin. Only twenty minutes previously he had chatted with a ward attendant, who had brought him a urinal, which he had used without incident. The cause of death was not determined, as permission for autopsy was denied.

The first patient was obviously in a critical condition when aureomycin treatment was started. Granulocytopenia, and shortly thereafter agranulocytosis, was demonstrated and presumably was the result of severe infection, although it may have been due to some other unexplained cause. The diabetic acidosis, though not severe, was not readily controlled. The pneumococci in this case were rapidly eliminated and could no longer be demonstrated at the time the first dose of penicillin was given, but A. aerogenes rapidly invaded the lungs and the blood.

The death in the second case remains unexplained and occurred after the patient was showing favorable progress similar to that noted in all the other patients following aureomycin therapy. The possibility of some episode related to his previous cerebral injury cannot be eliminated, but it did not produce any obvious manifestations. Furthermore, there was no indication of any untoward reactions from the aureomycin injections other than the local pain and tenderness from the

intramuscular injections in either of these 2 patients or in any of a large number of other patients who received similar parenteral injections for various conditions.

COMPLICATIONS

The only complications of the pneumonia noted in any of the patients who recovered have already been referred to in other connections. A sterile pleural effusion was demonstrated in 1 patient (J. A., chart 5) and was suspected but could not be demonstrated in another (M. C., chart 4), and an unexplained episode of fever and leukocytosis without symptoms followed apparent recovery in a third patient (M. McC., chart 6).

TOXIC EFFECTS OF AUREOMYCIN

The only significant untoward effects that resulted from oral aureomycin therapy were those referable to the gastrointestinal tract. Only 6 of these patients had nausea and vomiting; however, this was not sufficient to interfere with therapy, although the dose was reduced in some instances. Seven patients, including 5 of those who had some vomiting, passed large and bulky stools, usually two or four a day, which only occasionally became watery. In 19 patients there were no untoward effects from the oral preparations used. It is of interest that the gastrointestinal symptoms seemed to be much less frequent in the present series of patients than they were in those who were treated with aureomycin orally for primary atypical pneumonia,[2c] but this may be only coincidental.

The intramuscular doses were accompanied with moderate pain that lasted for about half an hour, and there was residual local tenderness for several hours. In 1 of the 4 patients receiving the large intravenous doses there was extravasation of some of the solution of aureomycin at the time of the fourth injection and this resulted in some redness, tenderness and swelling along the course of the vein for several inches and later there was slight edema of the forearm. This all cleared in a few days.

There were no instances of fever or rash and no evidence of toxic effects on the blood, kidneys, liver or nervous system attributable to either the orally or the parenterally administered aureomycin in any of the patients.

RESULTS OF SEROLOGIC TESTS

Agglutination tests with antigens prepared from homologous and heterologous types of pneumococci were carried out in the acute and convalescent phase serums of 20 patients. Agglutinins for pneumococci of the homologous types were demonstrated in titers ranging from 1 : 2 to 1 : 16 in the convalescent phase serums of 11 of these patients, including 5 who had positive blood cultures. The other 10 patients in whose

serums agglutinins could not be demonstrated included 3 who had pneumococcemia. However, the agglutination test, as used here, is not a very sensitive one for the demonstration of pneumococcus antibodies.[7]

Tests for cold agglutinins, Streptococcus MG agglutinins and anti-influenza A and B hemagglutinins were carried out in 26 of the patients. Cold agglutinins developed in low titer in 1 patient, G. G., and were present in high titer in both acute and convalescent phase serums in another. The latter was the patient N. G., who had asthma. Some of the details of both of these cases have been presented elsewhere.[2c] No significant titers or rises in titer of agglutinins for Streptococcus MG were found in any of the patients. A significant rise in titer of antibodies for influenza A was demonstrated in 3 patients, including G. G., in whom cold agglutinins also developed. The illness in these 3 patients occurred during the latter half of March 1949, when influenza A was prevalent in this community.

COMMENT

The present study was part of a general investigation of the range of effectiveness of aureomycin in acute pneumonias of diverse origin. The cases presented in this paper form a fairly uniform etiologic group, perhaps more so than any of the other prevalent types of pneumonia. They were, therefore, particularly suitable for a therapeutic evaluation. To be sure, the sulfonamides, and more particularly penicillin, have already proved to be highly effective in such cases, and rarely does the latter fail to bring about a cure in uncomplicated cases of this disease. It was, nevertheless, of interest to include the pneumococcic pneumonias in any general test of the therapeutic range of an effective antibiotic, and it seemed all the more justified after the initial favorable results were demonstrated.

The clinical and laboratory data that have been presented indicate clearly that aureomycin given either orally or intravenously is highly effective in the treatment of pneumococcic pneumonia. The results in the individual cases were quite decisive, and the beneficial effects were demonstrated with great regularity in all patients. The bacteriologic findings with respect to the disappearance of pneumococci from the sputum appear to be even more impressive than the results of similar

7. (*a*) Finland, M.; Spring, W. C., Jr., and Lowell, F. C.: Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, J. Clin. Investigation **19**: 179-199 (Jan.) 1940. (*b*) Finland, M.; Strauss, E., and Peterson, O. L.: Antibody Response of Patients with Pneumococcic Pneumonia Treated with Sulfadiazine and Sulfathiazole, Ann. Int. Med. **16**: 1-16 (Jan.) 1942. (*c*) Winkler, A. W., and Finland, M.: Antibody Response to Infections with the Newly Classified Types of Pneumococci (Cooper), J. Clin. Investigation **13**: 109-120 (Jan.) 1934.

studies in patients treated with sulfonamides [8] or with penicillin.[9] Furthermore, in the present cases the effectiveness of aureomycin did not seem to be dependent on the stage of the disease when the antibiotic was given and no suppurative pneumococcal complications developed. There were no cases, however, in which such suppurative complications were already present at the time when the aureomycin was started. In the 2 fatal cases the deaths were not the result of any failure to influence the pneumococcal infections.

Although penicillin treatment was not given in any parallel and comparable cases in this study, results in the present cases may be considered entirely comparable to those which have been observed here and elsewhere in similar patients treated with adequate doses of penicillin. The latter antibiotic may have the advantage of simplicity of administration, generally lower toxicity and, for the present at least, lower cost. Aureomycin, nevertheless, may prove advantageous under certain circumstances, particularly in cases of mixed etiology, in which the pneumococcus is only one of the causative agents, or in patients who are sensitive to penicillin or possibly in a rare case, if there be such, in which the causative pneumococcus is relatively resistant to penicillin. Further studies on the effect of aureomycin in patients with suppurative complications should also be of interest, but such cases were not available during the course of this study.

CONCLUSIONS

The clinical and laboratory data which have been presented indicate that aureomycin hydrochloride given either by mouth or intravenously is highly effective in the treatment of pneumococcic pneumonia.

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9. Ory, E. M.; Harris, H. W.; Meads, M.; Wilcox, C., and Finland, M.: Bacteriologic Studies of the Sputum in Patients with Pneumococcal Pneumonia Treated with Penicillin, J. Lab. & Clin. Med. **31**: 409-422 (April) 1946.

AUREOMYCIN THERAPY OF NONPNEUMOCOCCIC AND NONTUBERCULOUS BACTERIAL PULMONARY INFECTIONS

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THE RANGE of activity of aureomycin includes a wider variety of the known causative agents of pneumonia than that of any of the earlier effective chemicals or antibiotics.[1] Clinical trials were, therefore, undertaken of the use of aureomycin in all types of nontuberculous pneumonia and other severe acute infections of the respiratory tract that were available for study. In separate communications, we have presented the results of aureomycin treatment in cases of primary atypical (virus) pneumonia,[2] in cases of pneumococcic pneumonias [3] and in a variety of other cases which includes influenza and other severe acute infections of the respiratory tract and pneumonias in which a likely causative bacterial agent could not be identified.[4] In this paper are presented the results of aureomycin therapy in cases of the nonpneumococcic and nontuberculous bacterial infections of the lungs.

MATERIALS AND METHODS

Selection of Cases.—Two groups of cases were studied and treated. Group I includes 13 patients with acute pneumonia in whom cultures of sputum obtained before any therapy was given yielded predominant or pure growths of pathogenic

This study was aided by a grant from the United States Public Health Service.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Duggar, B. M., and others: Aureomycin: A New Antibiotic, Ann. New York Acad. Sc. **51**:175-342 (Nov. 30) 1948.

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3. Gocke, T. M.; Collins, H. S., and Finland, M.: Aureomycin Treatment of Pneumococcic Pneumonia: Clinical and Laboratory Studies on Thirty-Three Patients, Arch. Int. Med., this issue, p. 857.

4. Finland, M.; Wells, E. B.; Collins, H. S., and Gocke, T. M.: Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections, With and Without Pneumonia, Am. J. Med., to be published.

bacteria other than pneumococci. Most of these patients had an antecedent illness which was consistent with the diagnosis of "clinical influenza" and which occurred during March 1949, when proved influenza virus infections were prevalent in this community. None of these patients had received any antimicrobial agents before the administration of aureomycin was started, and they were acutely ill, with physical and roentgen signs of pneumonia at the time. Four of these patients were treated in nearby hospitals, and the others were from the medical wards of the Boston City Hospital. Group II includes 20 patients with infections that can best be characterized as "nontuberculous bronchopulmonary suppuration." These patients were all from the adult medical wards of the Boston City Hospital. All but 1 of them had been treated with large doses of other antimicrobial agents for varying periods before aureomycin therapy was started and had obtained only temporary benefit or none at all from the previous therapy. They were all acutely ill; some of them were also chronically ill, and all but 5 were febrile at the time aureomycin was started. In each case, pathogenic bacteria other than pneumococci were obtained in abundance or in pure growth from cultures of the sputum before the use of aureomycin was started.

Bacteriologic Studies.—Blood cultures were made just before aureomycin therapy was initiated and at irregular intervals during its administration. Stained smears and aerobic cultures were also made from carefully collected and freshly raised sputum before and at intervals during and after the aureomycin therapy. The predominant organisms were isolated in pure culture and tested for sensitivity to aureomycin by a serial dilution method either in suitable liquid mediums or on the surface of suitable agar mediums containing aureomycin.[5] Some of the cultures were done in the bacteriologic laboratory of the Mallory Institute of Pathology by Marion E. Lamb and A. Kathleen Daly; most of the sputum cultures and all the tests for aureomycin sensitivity were done by Janice M. Bryan and Clare Wilcox.

Serologic Tests.—Blood for serologic tests was obtained before and at suitable intervals after administration of aureomycin was started in all of the patients of group I and in some of those in group II. Tests for cold agglutinins, Streptococcus MG agglutinins and antihemagglutinins for the PR8 strain of influenza A and the Lee strain of influenza B organisms were done in all serums by the same methods as those used in the other collateral studies.[2] These tests were carried out by Mildred W. Barnes.

Dosage.—Almost all the aureomycin was given by mouth in the form of capsules, each containing 250 mg. of the crystalline hydrochloride, but occasional patients received some or all of the oral doses of the antibiotic in the form of the aureomycin base. One patient (case 15) received only intravenous injections of aureomycin hydrochloride, 500 mg. daily in 1,000 or 1,500 cc. of a 5 per cent solution of dextrose in water, and a second patient (case 7) received similar therapy for four days, after which he was treated orally. The dosage used to initiate the oral therapy in the patients of both groups was as follows:

Starting Dosage	Number of Patients	
	Group I	Group II
1.0 Gm. every 4 hours	5	11
1.0 Gm. every 6 hours	4	2
0.5 Gm. every 4 hours	2	6
0.5 Gm. every 6 hours	2	..

5. Paine, T. F., Jr.; Collins, H. S., and Finland, M.: Bacteriologic Studies on Aureomycin, J. Bact. **56**:489-497 (Oct.) 1948.

This dosage was later revised in many instances, the larger doses being reduced after the patient improved or if there was intense vomiting and the smaller doses increased if the patient did not improve promptly.

All the aureomycin was provided by the Lederle Laboratories, Division American Cyanamid Company, through the courtesy of Dr. Stanton M. Hardy.

ACUTE BACTERIAL (NONPNEUMOCOCCIC) PNEUMONIA

Some of the relevant clinical and laboratory findings in the 13 cases of acute bacterial pneumonia are listed in table 1. The patients were mostly young adults, but 4 of them were 60 to 76 years old; 8 of the 13 were men. The predominant organism isolated from the pretreatment sputum was either a beta hemolytic streptococcus, hemolytic Staphylococcus aureus or both in 11 of the patients; a hemolytic streptococcus and Klebsiella pneumoniae (Friedländer's bacillus) type A in 1 patient and Hemophilus influenzae in another. All the blood cultures taken in these cases yielded no growth.

Relation of the Pneumonia to Influenza Virus Infections.—There was evidence of the prevalence of influenza virus infection (mostly influenza A) in this community during the month of February and March 1949, most of the cases occurring during the latter month. The onset of the pneumonia in the present group of patients occurred during March 1949 in 9 cases (1 to 6, 8, 10 and 11), in April in 2 (7 and 9), in June 1949 in 1 (case 12) and in December 1948 in 1 (case 13). Except in the last 2 cases there was a history of antecedent systemic symptoms and symptoms referable to the upper respiratory tract compatible with a diagnosis of clinical influenza. This illness began from one to six days before the time of onset of the symptoms of pneumonia in cases 1 to 5 and from one to four weeks earlier in the remaining cases, the longest interval being in the cases in which pneumonic symptoms began during April.

Tests for hemagglutinin inhibition of influenza A and B organisms were made on the serums obtained during the acute and convalescent phase of the pneumonia in 12 of the 13 patients. The results are shown in table 1. There was conclusive evidence of influenza B infection in case 1 as indicated by a marked rise in titer of antibodies for the Lee strain and by the isolation of a strain of influenza B virus from the washing from the throat. In cases 2, 3, 4 and 5 there was serologic evidence of influenza A infection which, in case 2 was confirmed by the isolation of a strain of influenza A virus from the garglings obtained at the time of admission to the hospital. Elevated titers strongly suggestive of recent infection with influenza A virus were found during the acute stage of the pneumonia in cases 6, 9 and 10 and a significantly elevated titer of anti-influenza B hemagglutinins was found in case 7. Slightly elevated titers that may represent recent infection with influenza B

TABLE 1.—*Relevant Data on 13 Patients with Acute Bacterial (Nonpneumococcic) Pneumonia Treated with Aureomycin*

				Condition When Aureomycin Therapy Was Begun						Effect on the Course of the Disease				
				Anti-Influenza Hemagglutinins		Day of Disease	Temp., °F.	White Blood Cells	Pulmonary Lesions		Estimated Severity	Aureomycin, Total Dose		Drop in Temperature Hr.	Symptoms Improved, Hr.	Lungs Cleared, Days	Estimated Benefit
Case	Sex	Age	Predominant Organisms in Sputum	A (PR8)	B (Lee)				Type	Lobes		Gm.	Days				
1	F	14	Str. β_2; Staph. aureus$_2$	32/32	8*/2048	3	103.4	10,400	B	Rml, Ll	Severe	71.5	18	3-7 days	2-7 days	9-16‡	Good
2	M	72	Str. β_2; K. pneumoniae A$_8$	8*/256	8/8	4	103.0	10,800	B	Rum	Severe	20.0	5½	12-24	12-24	3-14‡	Excellent
3	M	15	Str. β	16/128	8/4	5	103.2	4,300	B	Lu	Moderate	14.5	4	12-24	12-24	2-5	Excellent
4	F	23	H. influenzae	128/256	4/4	3	103.8	15,300	B	Rl	Moderate	10.0	2½	12-48	12-48	3-7	Good
5	M	21	Str. β	8/32	16/16	6	105.0	9,000	B	Ll	Moderate	16.0	5	12-48	24-72	3-5	Good
6	F	34	Str. β_2	64/64	8/8	2	105.0	16,100	L	Rml	Severe	17.0	5	24	24-48	7-14	Good
7	M	64	Str. β_{12}; Staph. aureus$_8$	0/0	128/64	1	101.0	9,800	L	Ll	Moderate	2†+15	7	12-96	1-6 days	3-7	Good ?
8	F	22	Staph. aureus	0/0	32/32	4	105.0	8,900	B	Ll	Moderate	8.0	3	12-36	24	4-7	Excellent
9	M	15	Staph. aureus$_8$	128/128	16/16	2	102.0	11,700	L	Ll	Moderate	9.0	4½	12	12-24	2-5	Excellent
10	F	76	Str. β	256/128	4/4	3	101.0	11,500	B	Rl	Mild	6.0	2	18-24	12-24	4	Good ?
11	M	42	Str. β_2; Staph. aureus$_8$	.....	.....	2	104.0	15,800	B	Rl	Severe	24.0	4½	12	12-24	4-5	Excellent
12	M	17	Str. β_2	8/8	32/32	7	103.4	11,800	L	Ll	Moderate	9.5	5	12-48	18-36	2-5	Excellent
13	M	60	Str. β_1; Staph. aureus$_8$	16/16	4/4	2	105.0	14,500	B	Rl	Severe	11.0	5½	24-48	24-48	3-4	Excellent

Explanations and abbreviations: Organisms: Subscripts indicate aureomycin sensitivity in micrograms per cubic centimeter (complete inhibition). Anti-influenza hemagglutinins: The titers are given (acute/convalescent) as the reciprocal of the highest final dilution of serum; 0 = <4; * homologous virus isolated at this time. Day of disease refers to onset of pneumonia; antecedent influenza or other acute respiratory disease began at about the same time in cases 1, 2, 3, and 13—6 and 3 days earlier, respectively, in cases 4 and 5 and from one to four weeks earlier in the other cases. Pulmonary lesions: B, bronchopneumonia (atypical pneumonia); R, right; L, left; u, upper; m, middle; l, lower. Effect on Course: The first of 2 numbers represents time from first dose of aureomycin to the first major persistent drop in fever, improvement in symptoms or definite evidence of clearing of the lungs; the second numbers indicate, respectively, the interval to the time when the patient became completely afebrile and symptom free and the lungs were clear by both physical and roentgen examination.

† This patient's treatment was started with daily intravenous injections of 500 mg. (total 2 Gm.); all other doses were given by mouth.

‡ There was a sterile empyema in case 1 and probably some abscess formation in the lung in case 2; the course in these cases is shown in charts 1 and 2, respectively.

virus were also obtained in cases 8 and 12. In all, therefore, there was among these 13 patients definite evidence of influenza virus infection in 5 patients (4 with A and 1 with B organisms), titers strongly suggestive of similar recent infections in 4 others (3 with A and 1 with B organisms) and possibly in 2 additional cases (both with B organisms).

Results of Other Serologic Tests.—Tests for cold agglutinins and for Streptococcus MG agglutinins were carried out in serums taken before treatment was started and at intervals thereafter in all but 1 (case 11) of these patients. Cold agglutinins could not be demonstrated in the lowest dilution tested (1 : 10 final) in any of the serums of 11 of these patients. In case 3, there was a titer of 1 : 40 in the serum obtained on the day before treatment was started; this was the fourth day of illness (the influenza and pneumonia were considered to have begun on the same day in this case), and the same titer was found in serums obtained through the next six weeks. The titer of Streptococcus MG agglutinins rose in this patient from 1 : 10 to 1 : 40 during this period. One other patient (case 4) showed an increase in titer of Streptococcus MG agglutinins from 1 : 20 to 1 : 80. The first blood in this patient was obtained on what was estimated to be the third day of the pneumonia and the ninth day after the onset of symptoms of influenza, and the rise was demonstrated one week later. No cold agglutinins could be demonstrated in any of the serums from this patient. In the remaining patients, the tests for Streptococcus MG agglutinins were either entirely negative (3 cases) or showed the same titers, ranging from 1 : 10 to 1 : 40, in all specimens taken during the acute and convalescent phases. The results of these tests, together with those for influenza antibodies, were interpreted as offering no support for the diagnosis of primary atypical (virus) pneumonia in any of these patients.

Condition of the Patients When Aureomycin Was Started.—Treatment with aureomycin was begun during the first three days of the pneumonia in 8 cases, on the fourth or fifth day in 3 and on the sixth or seventh day in the remaining 2 cases. As already mentioned, none of these patients had previously received any antimicrobial therapy. All the patients were acutely ill and febrile when the first dose of aureomycin was given. The temperature at this time ranged between 101 and 105 F. and was 103 F. or higher in 10 of the 13 patients. The total leukocyte counts varied between 4,300 and 16,100, and in 9 of the patients these counts were below 12,000.

The pulmonary lesion as determined by physical examination and from the roentgenograms was limited to a single lobe in 10 cases and to two contiguous lobes of the right lung in 2 cases; it was bilateral in only 1 case. In most of the cases the lesions appeared in the roentgenograms as mottled or patchy areas of density with predominantly peri-

bronchial distribution or radiating out from the hilar region. In 4 cases, however, the physical and roentgenographic signs were those of lobar consolidation similar to those characteristically found in pneumococcic pneumonia. There were also musical rales heard bilaterally in most of the cases and showers of crepitant rales over the consolidated areas. Most of the patients had severe cough and complained of soreness over the sternum, but several complained of pleuritic pain and a loud friction rub was heard in 5 patients.

An attempt was made to estimate the severity of the illness in each case from the general appearance of the patients, the symptoms and other

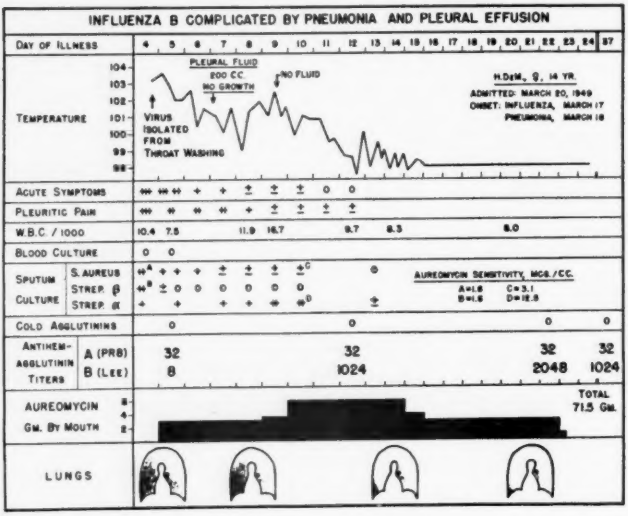

Chart 1.—Course, treatment and relevant laboratory data in case 1.

observations. The illness at the time aureomycin was started was considered to be severe in 5 cases, moderate in 7 and mild in 1.

Aureomycin Therapy.—One of the patients who had a complicating pleural effusion received a total of 71.5 Gm. in eighteen days (case 1, chart 1). The total dose for the remaining 12 patients ranged between 6 and 24 Gm. and was given over a period of two to seven days. The average total dose of these 12 patients was 13.3 Gm. in an average of four and one-half days. One patient (case 7) received four daily doses of 500 mg. of aureomycin intravenously, and oral doses were used to continue the therapy in this case.

Effect of Aureomycin on the Course of the Disease.—The course of the fever and symptoms after aureomycin was started was similar in the present cases to that observed in the aureomycin-treated cases of pneumococcic pneumonia.[1] A major drop in the temperature occurred, except in case 1, in the first twelve to twenty-four hours, and only 2 patients had any fever after the second day of therapy. In case 1 there was a sterile pleural effusion and the temperature dropped gradually during the first three days, but this was followed by a second bout of fever, lasting four more days. In case 7 there was intermittent fever associated with pyrogenic reactions to intravenous injections during the second and fourth day.

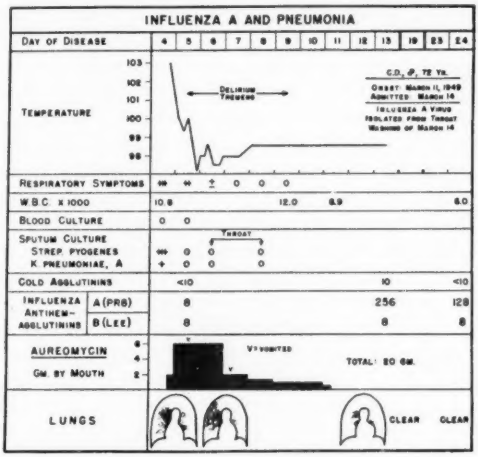

Chart 2.—Relevant data in case 2.

Symptomatically, all the patients were noticeably improved by the end of the first twenty-four hours; 10 were entirely free of symptoms by the end of the second day, and the remaining 3 continued to have pleuritic pain, raise blood-tinged sputum or had other minor complaints for three, six and seven days, respectively, after aureomycin was started.

The lungs cleared rapidly, as judged by the physical and roentgen observations. There was definite evidence of clearing of the lungs in all but 2 of the patients within the first four days. The lungs were entirely clear roentgenographically by the end of a week after the first dose in 10 patients. In case 1, in which there was a pleural effusion; in case 6, in which there was atelectasis of the middle lobe of the right lung, and in case 2 (chart 2), in which there was probably some abscess

formation in the upper lobe of the right lung, complete clearing of the pulmonary fields roentgenologically was delayed until fourteen to sixteen days after the use of aureomycin was started.

Effect on Bacteriologic Findings in the Sputum.—The predominant organisms found in the sputum were rapidly cleared after the start of aureomycin treatment, although the results in some cases were not so striking as they were in all cases of pneumococcic pneumonia.[1] Cultures of sputum were made at frequent intervals during and after treatment in 9 of the cases. Hemolytic streptococci present in the sputum before treatment could no longer be demonstrated after the first day of auero-mycin therapy in 4 cases and after the second, third and fourth day in 1 case each. In case 7, the hemolytic streptococci were still present in cultures of the sputum after seven days of therapy. There were 2 patients who continued to raise rusty sputum, 1 for 4 days and the other for six days after aureomycin was started; hemolytic streptococci could not be recovered from the sputum after the first day in the former and after three days in the latter.

Hemolytic Staphylococcus aureus, present in large numbers in the cultures made before treatment, could no longer be demonstrated after the first day of aureomycin therapy in 1 patient and after three or four days in 4 others. In case 1, these organisms were obtained in diminish-ing numbers during seven days of therapy but could not be obtained from subsequent sputum specimens. K. pneumoniae in case 2 could not be recovered from any specimens obtained after aureomycin was started.

Tests for sensitivity to aureomycin were carried out on most of the strains, and the results are indicated in table 1. It is of interest that the hemolytic streptococcus in case 7 was the least sensitive of the strains tested and required 12.5 micrograms for complete inhibition. K. pneumoniae was sensitive to 6 micrograms, and all other strains of hemo-lytic streptococci and staphylococci were completely inhibited by 3 micro-grams or less. The sensitivity of all strains of the same organisms isolated from the same patient after aureomycin therapy was started was the same as before the start of treatment, and no evidence of increase in resistance could be found in any of the strains from this group of patients.

NONTUBERCULOUS PULMONARY SUPPURATION

The second group consists of 20 cases of the type in which the results of therapy at best are very difficult to evaluate. The patients ranged in age from 37 to 78 years, and only 5 were less than 50 years old. All but 3 of the patients were male. There was a history of underlying productive cough for varying periods in almost all these cases, and other serious underlying conditions played a significant or major role in most of them.

In almost all these cases the treatment with aureomycin was undertaken during an exacerbation of the chronic underlying bronchopulmonary infection, usually following some acute infection of the upper respiratory tract or pneumonia. The history of the underlying respiratory disease was usually long and complicated and many forms of therapy had been used. During the acute episode, except in case 24, treatment with other antimicrobial agents had been given for varying periods ranging from three days to several months before aureomycin was started. Aureomycin was given in these cases for varying periods while either some other agents were being continued or some other antimicrobial agents were given after it became apparent that no further benefit could be expected from the aureomycin.

In order to simplify the presentation, the data most relevant to the antimicrobial therapy and particularly to the evaluation of the effect of aureomycin in each case have been listed in table 2. Some of the pertinent aspects will be summarized briefly.

Condition of the Patients When Aureomycin Was Started.—The severity of the disease in each of these patients was graded on the basis of the available clinical findings and from the general appearance at the time when aureomycin was started. Six of the patients were considered to be moderately ill; 10 were severely ill, and 4 were thought to be critically ill at the time. All but 5 of the patients were febrile, and most of them had slight to moderate leukocytosis.

The pulmonary lesion in most of the cases consisted of rather diffuse areas of patchy density in both lungs, particularly in the bases. There was also evidence clinically of chronic bronchitis and bronchiectasis in most of the cases. In a few cases there were large solitary or multiloculated abscess cavities in a single lobe with pneumonitis in the surrounding lung, and fluid levels within the cavities were visualized in the roentgenograms from time to time in such cases.

Bacteriologic Observations.—All the blood cultures taken before administration of aureomycin was started showed no growth. A positive blood culture for type A K. pneumoniae had been obtained previously in case 17, before that patient received streptomycin, but subsequent blood cultures in this case showed no growth.

The bacterial flora in the sputum of the patients varied considerably, but in most of them there were one or two organisms which were predominant in the pretreatment cultures. Coagulase-positive strains of hemolytic Staph. aureus were the most frequent; these strains were all highly resistant to penicillin, the patients having previously been treated with massive doses of this antibiotic. Most of these strains of staphylococci were susceptible to aureomycin, being completely inhibited by 3 micrograms per cubic centimeter or less, but two of them

TABLE 2.—*Relevant Data on 20 Patients with Nontubercu*

Case	Sex	Age	Predisposing Factors	Condition When Treatment with Aureomycin Was Started					
				Day of Disease	Previous Therapy: Agent	Previous Therapy: Days	Predominant Organisms	Extent of Lung Involved	Temperature, °F.	White Blood Cells
14	F	51	Diabetic acidosis; pyelonephritis	10	Penicillin	3	Staph. aureus$_{32}$; Str. β_8	B, bilateral	103	21,000
15	M	60	Hypernephroma; uremia	? 31 ? 3	Penicillin	3	Staph. aureus$_{32}$; Ps. aeruginosa$_{64}$	B, bilateral	100	13,000
16	M	78	Bronchiectasis	32	Penicillin Sulfadiazine	26 21	Staph. aureus$_{32}$; Ps. aeruginosa$_{100}$	B, Rlm, empyema	105	9,400
17	M	61	Chronic bronchitis	15	Penicillin Sulfadiazine Streptomycin	9 9 5	K. pneumoniae A$_8$; Staph. aureus$_{32}$	L, Ru, abscesses	103	15,900
18	M	57	Bronchiectasis	20	Penicillin	10	H. influenzae$_8$	B. bilateral	102	19,900
19	M	38	Hepatic cirrhosis; delirium tremens; diabetes	? 8	Penicillin Streptomycin	4 3	A. aerogenes$_{100}$; Paracolon$_{200}$	L, Rl	104	1,900
20	F	48	Chronic alcoholism; hepatic cirrhosis; jaundice	>57	Penicillin Sulfadiazine	46 28	Staph. aureus$_{32}$; Str. β_8; Enterococcus$_8$	B, Lul, abscesses, empyema	102	30,000
21	M	66	Chronic alcoholism; diabetes; impetigo; paronychia	15	Penicillin Sulfadiazine	8 7	Staph. aureus$_{32}$	B, Ll, abscesses	102	21,000
22	M	55	Bronchiectasis; decubitus	31	Penicillin Sulfadiazine Streptomycin	30 24 4	Staph. aureus$_8$	B, bilateral, abscesses	101	15,800
23	M	56	Cerebral hemorrhage; hemiplegia; cardiac failure	15	Penicillin Sulfadiazine	18 15	Staph. aureus$_{32}$; Str. β_1; Ps. aeruginosa$_{50}$	B, bilateral, abscesses	103	3,100
24	M	58	Chronic bronchitis; bronchiectasis	3	None	..	Pneumococcus (type 20)$_2$; P. vulgaris$_{200}$	B, bilateral, atelectasis	103	16,000
25	M	57	Chronic alcoholism	56	Penicillin Sulfadiazine	4 23	A. aerogenes$_{25}$; mixed flora	Abscess, Ru	99	6,200
26	M	46	Hemoptysis	6 mo.	Penicillin Sulfonamides	25 23	Staph.aureus$_{64}$; A. aerogenes$_{100}$	Abscess, Lu, ? brain abscess	98	6,100
27	M	49	Bronchiectasis; emphysema	28 yr.	Penicillin	7	Staph. aureus$_{32}$; P. vulgaris$_{200}$; A. aerogenes$_{200}$	B, bilateral	98	12,000
28	M	52	Foreign body (tooth) inhaled	38	Penicillin Sulfadiazine	14 7	P. vulgaris$_{200}$; A. aerogenes$_{25}$	Abscess, Lu	101	12,000
29	M	57	Bronchiectasis emphysema	Many years	Penicillin	30	H. influenzae$_{32}$; A. aerogenes$_{12}$	Bilateral	98	12,900
30	M	65	Postpneumonectomy; empyema	24	Penicillin	15	A. aerogenes$_{25}$	Empyema	100	12,000
31	F	37	Pulmonary fibrosis; emphysema; asthma	12 mo.	Penicillin Sulfadiazine	150 7	Staph. aureus$_{64}$; P. vulgaris$_{100}$	B, bilateral	102	5,000
32	M	64	Hemoptysis	6 mo.	Penicillin	22	Staph. aureus$_8$	Abscess, Lu B, Lul	100	12,000
33	M	61	Prostatic carcinoma; pyelonephritis; bronchiectasis	20	Penicillin Sulfonamides	18 13	Staph. aureus$_{25}$ Ps. aeruginosa$_{200}$	B, bilateral	98	13,000

Explanations: Day of disease refers to the particular episode under treatment in the chronic cases. Other abbreviations are used as in table 1.

Estimated Severity	Aureomycin, Total Dose		Additional Therapy		Course and Complications Under Aureomycin	Estimated Benefit from Aureomycin
	Gm.	Days	Agent	Days		
Critical	54	11	Penicillin	19	Steady defervescence and improvement in 9 days; Ps. aeruginosa$_{200}$ and Monilia replaced flora of sputum; P. vulgaris$_{200}$ persisted after A. aerogenes$_{80}$ cleared from urine (on catheter drainage)	Slight
Critical	4 i.v.	8	Penicillin	8	Improved markedly first 2 days; then pulmonary edema developed; Ps. aeruginosa$_{200}$ replaced staphylococci; died eighth day	Slight, temporary
Severe	72	12	.....	..	Afebrile in 3 days; improved markedly in 4 days; empyema cleared; lungs cleared 5 to 10 days; staphylococci rapidly cleared from sputum	Good
Severe	72	13	Penicillin	>13	K. pneumoniae cleared from blood on streptomycin before aureomycin was begun but were found off and on in sputum and at operation and did not increase in resistance; large abscess drained surgically; gradually improved	Doubtful
Moderate	28.5	10	Penicillin	7	H. influenzae replaced by A. aerogenes$_{25}$ then by P. vulgaris$_{200}$; fever and symptoms improved steadily for 4 days; lungs cleared slowly (by roentgenograms) after 6 days	Good ?
Severe	0.8 i.m. 73	1 17	Penicillin Streptomycin Sulfadiazine	18 2 >20	Type A K. pneumoniae, cleared from sputum before aureomycin was started; fever persisted throughout therapy, but patient gradually improved after 4 weeks	Slight ?
Severe	30	12	Chloramphenicol	35	Staphylococci and streptococci promptly replaced by P. vulgaris$_{200}$ and Monilia; no effect from chloramphenicol, 120 Gm. after aureomycin ended; partial resection and drainage with slow improvement	None ?
Severe	126	32	Penicillin Sulfadiazine	41 39	Marked and steady improvement after aureomycin was added to therapy; staphylococci cleared slowly in 17 days; replaced by Ps. aeruginosa$_{200}$; afebrile after 6 days; lungs cleared almost completely	Moderate
Critical	65	12	.....	..	Staphylococcic pneumonia followed D. pneumoniae type 20 pneumonia with bacteremia that was cleared on previous therapy; markedly improved and afebrile in 3 days; lungs cleared but marked fibrosis resulted in cardiac symptoms	Good ?
Critical	53	10	Sulfadiazine Chloramphenicol	4 9	Dramatic immediate improvement; P. vulgaris$_{200}$ rapidly replaced flora of sputum and stayed in urine (catheter drainage); chloramphenicol given when afebrile failed to clear proteus (sensitive to 20 μg/cc.) from urine or sputum	Moderate
Severe	40.5	17	Chloramphenicol	4	D. pneumoniae cleared rapidly but P. vulgaris persisted in sputum; marked improvement in 36 hours, then gradual for 9 days; chloramphenicol later failed to clear P. vulgaris from sputum	Moderate
Moderate	37.5	17	.....	..	Amount and odor of sputum decreased rapidly (also had bronchoscopy and postural drainage); only P. vulgaris $_{200}$ and A. aerogenes$_{25}$ in sputum after aureomycin was started	Slight
Severe	21	7	.....	..	Afebrile throughout; staphylococci cleared rapidly; A. aerogenes persisted and P. vulgaris$_{200}$ appeared; lung cleared partially; signs of ? cerebellar abscess on entry and persisted	Slight ?
Severe	54	19	Chloramphenicol	9	Sputum decreased in amount and became less purulent; A. aerogenes and P. vulgaris persisted and were not affected by chloramphenicol; remained afebrile	None ?
Moderate	62.5	14	Penicillin	8	Steady improvement; became afebrile; amount and odor of sputum reduced; also had bronchoscopy and postural drainage when aureomycin was started; almost cleared by roentgenograms	Moderate
Moderate	33	12	.....	..	Sputum reduced in amount and became less purulent; H. influenzae cleared promptly; improved generally and gained weight	Good
Severe	1 i.pl. 100	22 23	Penicillin	26	Repeated intrapleural instillations of gradually increasing amounts 5-100 mg. (buffered) of aureomycin; numbers of organisms dropped each time but then increased again; required repeated open drainage; sensitivity of A. aerogenes in pleural fluid decreased from 25 to 100 μg	Slight, temporary
Severe	222 (intermittent)	46	Streptomycin	30	Had 4 courses of aureomycin (longest 40 days); improved each time and relapsed when drug was stopped; died 12 months after first course	Slight, temporary
Moderate	115	31	.....	..	Improved for 3 days after bronchoscopy and postural drainage; afebrile and more rapid improvement on aureomycin; Staph. aureus persisted and sensitivity increased fourfold (was resistant to penicillin); lung healing, and sputum much decreased; A. aerogenes$_{100}$ and Ps. aeruginosa$_{200}$ appeared during second week and persisted	Moderate
Moderate	43	15	.....	..	Continued to cough and raise purulent sputum; staphylococci cleared slowly and Ps. aeruginosa later found in pure culture in sputum and urine	Doubtful

required 6 micrograms and one required 25 micrograms for complete inhibition. Hemolytic streptococci in large numbers were isolated from 3 patients and Hemophilus influenzae from 2 others; all these strains were sensitive to 3 micrograms per cubic centimeters or less.

There were 2 cases of type A K. pneumoniae pneumonia in this group. In both of them (cases 17 and 19) streptomycin and penicillin had been used before the aureomycin was started; in 1 of them the organisms were no longer demonstrable in the blood, and in the other they could not be obtained from cultures of the sputum after aureomycin was started. In each of the 2 cases there was extensive abscess formation which appeared to be progressing, and both patients were still acutely ill when aureomycin therapy was started. The strains of K. pneumoniae from both of these patients were highly sensitive to streptomycin before that antibiotic was given, and the strain isolated before aureomycin treatment in case 17 was just as sensitive to streptomycin as the original strain in that case.

In the remaining cases the predominant organisms were mainly of the type more frequently encountered in chronic infections of the urinary tract, namely, Aerobacter aerogenes, Proteus vulgaris and Pseudomonas aeruginosa. Most strains of these organisms were moderately to markedly resistant to aureomycin, requiring 25 to 200 micrograms per cubic centimeter for complete inhibition.

In case 24, Diplococcus pneumoniae type 20 was found in the initial sputum specimen and was identified in smears and cultures. The pretreatment sputum specimen, however, showed a predominance of gram-negative bacilli, and P. vulgaris also predominated in the surface cultures of this sputum.

Dosage.—Larger doses were used and were given over longer periods in these cases than in those of group I. The total oral dose varied from 21 to 222 Gm. given over periods ranging from seven to forty-six days. The patient who received the largest amount (case 31) was given aureomycin intermittently for one to three weeks at a time over a period of several months. In all the other cases the entire dose was given more or less continously. The intravenous route was used exclusively in case 15, 500 mg. being given daily for eight days. The average oral dose in the remaining 19 patients was 70 Gm. given over an average of seventeen days.

Effect of Aureomycin on the Clinical Course.—The effect on the clinical course is summarized in table 2 for each of the patients. Most of them showed some improvement in their general condition soon after the aureomycin was started, and in some of those who were severely or critically ill at the time the immediate improvement was dramatic. The temperature usually declined slowly. The sputum, in those in whom it was foul, lost its odor in most cases. The amount of sputum

raised was usually decreased markedly, and some of the patients stopped raising any sputum. The character of the sputum in other cases changed from purulent to mucoid.

Improvement in the pulmonary lesion as judged from the physical signs and the roentgenograms also varied considerably. There was marked and fairly rapid clearing in some of the cases, but in most instances this occurred slowly. Surgical drainage of abscesses was required in only 2 of the cases, including 1 case of K. pneumoniae infection (case 17).

Just how much of the improvement that was observed could be ascribed to the aureomycin was sometimes difficult to assess. In an occasional case drainage improved after bronchoscopy, and in other cases postural drainage was being carried out with good effects during the time that aureomycin was being given. Since similar procedures were also done in these and other cases during the antecedent therapy, which included systemic and aerosol administration of penicillin in many cases, it was felt that the aureomycin was responsible, in large measure for the observed improvement. A rough evaluation of the benefit derived from the aureomycin in each case is shown in the last column of table 2.

Two of the patients died. In 1 case (case 15) death resulted from hypernephroma and uremia, the latter already rather severe when the aureomycin was started. In this case there was marked improvement during the first two days of intravenous aureomycin therapy. In the other case (case 31) death occurred almost a year after the patient received the first course of aureomycin. This patient was almost moribund when the aureomycin was first given, and she was noticeably improved for several weeks at a time during and after each course of aureomycin.

Effect on the Bacteriologic Flora of the Sputum.—The effects of aureomycin treatment on the bacteriologic flora of the sputum in these cases were similar to those noted in the urine in cases in which treatment was given for infections of the urinary tract.[6] The susceptible strains were cleared rapidly in most cases and somewhat more slowly in others. In the majority of the cases relatively resistant organisms, usually P. vulgaris, A. aerogenes or Ps. aeruginosa, replaced the strains of sensitive organisms. Increase in resistance of strains of the same organisms isolated during or after the course of aureomycin was noted only in case 30. In this case aureomycin was given orally and was also instilled intrapleurally in increasing amounts over several weeks. After each intrapleural instillation the number of organisms in the exudate decreased markedly, as did the amount of exudate, but these changes were only temporary. In this case the strain of A. aerogenes when originally

6. Collins, H. S., and Finland, M.: Aureomycin Treatment of Urinary Tract Infections, Surg., Gynec. & Obst. **89**:43-48 (July) 1949.

isolated was sensitive to 25 micrograms of aureomycin per cubic centimeter, and the organisms obtained after several weeks required 100 micrograms for complete inhibition. In all other cases, all strains of the same organisms isolated before, during and after aureomycin therapy had the same sensitivity to this antibiotic.

Effect of Additional Antimicrobial Therapy.—In two thirds of the cases further therapy with sulfonamides or other antibiotics, singly or in combination, was given after the course of aureomycin was concluded or during the latter part of the aureomycin treatment. There was little if any additional beneficial effect observed from these agents either on the clinical course or on the bacteriologic findings. Of particular interest are the cases of 4 patients (cases 20, 23, 24 and 27) to whom chloramphenicol (chloromycetin®) was given in doses of 4 to 6 Gm. a day in attempts to clear the sputum of organisms, particularly P. vulgaris, that persisted during the aureomycin therapy. In none of these 4 cases was any additional beneficial effect on the clinical course, on the pulmonary lesion or on the bacteriologic findings observed during the administration of chloramphenicol.

TOXICITY

The untoward effects from aureomycin in the present cases were of the same character and frequency as those observed in other groups of cases that have been studied here. They were limited almost entirely to gastrointestinal symptoms. Vomiting or nausea occurred during oral therapy in 9 of the cases of group I and in 11 of those in group II. Loose and frequent bowel movements were experienced in a total of 5 cases in both groups, including those of 4 patients who also had gastric symptoms. There were also 2 cases in group II in which the patients complained of slight dizziness after more than a week of therapy. In a third case (case 32) of this group the tongue appeared red and smooth at the end of a thirty-one day course. The last 3 patients also vomited several times during the latter part of their therapy. There were 4 cases in group I and 7 in group II in which the patients experienced no untoward effects whatever.

It is of interest that among the patients who experienced nausea and vomiting from the aureomycin this was transient in some, occurred only after two or more days of therapy in others and in several was experienced only on the largest oral doses (1 Gm. every four hours) and did not occur after the dose was reduced to 0.5 Gm. every four hours. Among those who had some untoward gastrointestinal symptoms were 9 patients who received more than one lot of aureomycin, each preparation being given for three to seven or more days in doses of 1 Gm. every four or six hours. Five of these patients had these symptoms from only one of two lots and not from the other; 1 patient had them from

one of three and another from one of four lots and not from the other two and three, respectively. One additional patient received four lots, and another received six different lots; the former had untoward effects from two and the other from four of these lots.

The patient who received part of the aureomycin intravenously (case 7) experienced mild pyrogenic reactions from the second and the fifth dose, but there were no reactions in case 15 in which all of the aureomycin was given intravenously. One patient who received eight intramuscular injections of 100 mg. each during the first day had considerable local pain and tenderness. In case 30 there were no untoward reactions when small amounts of aureomycin were injected intrapleurally, but when 50 or 100 mg. was instilled the patient complained of a "hot sensation" in the chest that lasted several minutes.

In no instance was there any fever or rash that could be attributed to the aureomycin. There were no detectable untoward effects on the blood, kidneys, liver and nervous system in any of the patients.

COMMENT

The results of aureomycin therapy in these two groups of cases indicate clearly both the versatility and the limitations of this antibiotic in the treatment of nontuberculous bacterial infections of the lungs. In the acute cases of group I in which only sensitive bacterial strains appeared to be involved, the clinical results were uniformly good. Furthermore, the rapid disappearance of the susceptible organisms, although not quite so striking in these cases as they were in the cases of pneumococcic pneumonia, was nevertheless impressive. This served to confirm the impression that the observed benefits were indeed ascribable to the action of the aureomycin.

The only significant complication encountered in this group was a sterile effusion in case 1. This most probably represented a metapneumonic empyema which had been rendered sterile by therapy. The fluid obtained was purulent, contained 59,000 leukocytes per cubic millimeter, almost all of them polymorphonuclears, and showed no organisms on direct smear and no growth on culture. Two days later, an attempted thoracentesis in this patient yielded no fluid. There was also atelectatic collapse of most of the middle lobe of the right lung in 1 other patient, and this was only temporary. In case 2 these may have been early abscess formation which healed rapidly and completely.

In most of the cases of group II, extensive tissue damage was already present as the result either of some underlying bronchopulmonary disease or of the immediate acute infection that was not entirely arrested by antecedent therapy. The amount of benefit derived from the aureomycin in the individual cases appeared to depend largely on the nature of the offending organisms, their susceptibility to aureomycin and the

extent and character of the pulmonary lesions. In cases in which relatively resistant organisms were present from the start or appeared in predominant numbers, in which there were extensive suppurative lesions that were not draining adequately or in which there were more serious underlying lesions, the effects from aureomycin were slight or equivocal.

The findings in these cases do indicate, however, that some benefit may be expected from aureomycin in a considerable proportion of cases of nontuberculous bronchopulmonary suppuration after other antimicrobial agents, particularly sulfonamides, penicillin and streptomycin, either have failed completely or have given only partial or slight relief. The failure of organisms to develop resistance to aureomycin during the course of treatment, which is similar to penicillin in this respect, is an important feature of the treatment of protracted infections. The presence of other unhealed lesions or the improper drainage or absorption of suppurative foci, however, predispose to additional infections with insensitive organisms during treatment with aureomycin, just as they do during penicillin therapy.

Although chloramphenicol failed to bring about any additional improvement in the 4 cases of this group in which it was used after the aureomycin, no conclusions are justified concerning its effectiveness in similar cases if it were used in the same manner that aureomycin was used here or if it were used to initiate therapy in similar cases.

SUMMARY AND CONCLUSIONS

Aureomycin alone was highly effective in the treatment of a group of 13 cases of acute bacterial, nonpneumococcic pneumonias. Most of these cases probably occurred as complications of influenza viral infections.

The effects of aureomycin therapy in 20 cases of nontuberculous bacterial bronchopulmonary infection were variable. The best effects were observed in cases in which aureomycin-susceptible organisms were primarily concerned. The beneficial effects were limited, however, because of the replacement of some of these susceptible organisms by relatively resistant ones. In almost all these 20 cases the aureomycin was started after other antibacterial agents had been given without effect or with only limited benefit. Subsequent use of similar antibacterial agents in most of these cases, including chloramphenicol in 4, failed to produce any further appreciable beneficial effects.

STERNAL MARROW IN PATIENTS WITH METASTATIC CANCER

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SOME TIME ago the chance diagnosis of metastatic carcinoma first made by means of sternal aspiration stimulated my interest in the procedure and led to a search for further information. It seemed probable that metastatic tumor cells could be found in bone marrow more frequently than has been supposed if only the proper search were made. A study of bone marrow smears obtained by sternal aspiration from 32 patients with known or suspected metastatic carcinoma or sarcoma has been carried out in an effort to determine the pattern of reaction of the marrow to cancer. The findings of this study together with a brief review of the available literature are reported.

REVIEW OF THE LITERATURE

Literature in the English language concerning hematologic and cytologic observations in patients with cancer is sparse. Standard texts make only brief mention that occasionally tumor cells may be found on sternal aspiration.[1] I have been able to find few detailed studies of the cytology of tumor cells as shown on smears and imprints stained with Wright's and Giemsa stains.

Paul Ehrlich and Lazarus,[2] in their monograph on the histology of blood published in 1900, discussed the changes in the blood arising from tumors by citing 2 cases reported by Nathnagel and by Israel and Leyden. In the first case the peripheral blood showed "simple severe anemia" with isolated normoblasts, small marrow cells and a moderate leukocytosis. No mention was made of tumor cells in blood. At autopsy the skeletal system showed complete atrophy of bone marrow and replacement by tumor cells. As sternal aspiration did not become preva-

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1. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, 1946. Piney, A., and Hamilton-Paterson, J. L.: Sternal Puncture, ed. 3, New York, Grune & Stratton, Inc., 1946.

2. Ehrlich, P., and Lazarus, A.: Histology of the Blood Normal and Pathological, edited and translated by W. Myers, University Press, Cambridge, 1900.

lent until after 1930, the tumor cells which might have been discovered by study of the sternal marrow were not found ante mortem. In the second case there was the usual degree of anemia without an unusual leukocyte picture. Ehrlich cited a third case of Epstein's, in which there were considerable anemia, numerous nucleated red blood cells "both of the normo- and megaloblastic types," leukocytosis and increase in large mononuclear forms (description not given) without significant eosinophilia. Autopsy proved metastatic carcinoma of bone marrow. No additional observations of their own experience were recorded by Ehrlich and Lazarus.

Nordensen's [3] monograph published in 1935 contains a report of a study of sternal marrow from more than 160 patients, including some hematologically normal persons, some with primary blood dyscrasias and some with various other types of disease. Among the last-mentioned group were 17 patients with various types of cancer. In none of them did Nordensen directly describe tumor cells. In 2 instances he described "large granular cells with loose nucleus and peculiar shape and plentiful cytoplasm which is sometimes vacuolated and slightly basophilic with hypergranulation." These cells were not classified more specifically. In 10 of the 17 cases there was a shift to the left in the myeloid series; in the majority of cases the marrow was said to be "cellular"; in only 4 cases did he report numerous reticuloendothelial cells, and in 11 cases he stated that eosinophilic cells were "scarce," "rare" or "strikingly few." He cited Plenge as saying that both cancer and sepsis have an inhibitory effect on granulopoiesis and that there is no essential difference in marrow in patients with cancer with and without infection.

Rohr and Hegglin [4] studied and reported on the sternal marrow of 74 patients with malignant tumors; 10 had malignant cells in the smears. They described malignant cells as characterized by anisocytosis, an extraordinarily large nucleus with a large nucleolus and an increased ratio of nucleolus to nucleus. These authors asserted that a diagnosis may be made from a single cell in the smear if it is from a large cell type of tumor but that groups are necessary if the cells are from the small cell type tumor. They tested some of their cytologic characteristics by making direct smears from primary and metastatic nodules and staining with Wright's and Giemsa stains, as if the smears were from bone marrow. They expressed the belief that the appearance of the cells so obtained is identical with that of the tumor cells found on aspiration. Five of the patients with smears positive for cancer had bronchogenic

3. Nordensen, N. G.: Studies on Bone Marrow from Sternal Puncture, Stockholm, Börtzells, Esselte, 1935.

4. Rohr, K., and Hegglin, R.: Tumorzellen im Sternalpunktat, Deutsches Arch. f. klin. Med. **179**:61, 1936.

carcinoma; 2, gastric carcinoma; 1, prostatic carcinoma, and 2, retroperitoneal sarcoma.

Kreyburg and Poppe [5] aspirated marrow from 100 patients and made parallel series of smears and of sections of fixed and embedded preparations. They found tumor cells in preparations from 8 of the 100, and all 8 were patients who showed clinical and roentgenologic evidence of metastases. These authors did not describe the characteristics of the cells in detail but, rather, utilized histologic criteria of the tissue obtained in diagnosing the presence of malignant cells. From their study they concluded that the fixed and sectioned preparations are more useful in making such diagnoses. Three of the 8 patients with sections positive for tumor cells had carcinoma of the breast, 3 had carcinoma of the prostate gland, 1 had carcinoma of the stomach and 1 had multiple myeloma.

Schleicher,[6] too, utilized both the imprint and the histologic technic to point out the value of sternal aspiration in finding tumor cells. He also stated that fixation and sectioning give a greater number of positive diagnoses.

METHOD

As it was the purpose of this investigation to discover how often on routine examination by technics already widely used one may find tumor cells in the bone marrow, no special technics were used for the principal portion of the study.

The sternum was selected for aspiration, as it is my preferred site. The needle was inserted into the marrow cavity at the level of the second interspace. Approximately 0.25 to 0.5 cc. of marrow was aspirated and immediately flooded onto clean slides. In this way marrow "units" might be seen readily as light yellow-white flecks floating in the blood when the slide was held against the light. These units were picked out singly with applicator sticks and transferred to cover slips to make the conventional cover slip smears. Smears were stained with Wright's stain and counterstained with Giemsa stain.

From 10 to 20 preparations from each patient were scanned under low power and then under high power with dry and oil immersion objectives. General impressions were gained as to activity, types of cells predominating and presence or absence of tumor cells. At least 250 to 300 cells were counted for a differential count, but it was recognized that such differential counts are only approximations and ought not be considered absolute in any respect.

Cytologic criteria for malignancy were considered to be as follows:

1. The general structure and staining qualities of the cells are at variance with those of normal cells in normal bone marrow.

2. The cells are usually large, 15 to 25 microns.

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5. Kreyburg, L., and Poppe, E.: Tumour Cells in Sternal Bone-Marrow, Lancet **1**:593, 1940.

6. Schleicher, E. M., and Fahr, G.: The Value of the Sternal Portion of the Bone Marrow in Diagnosis, Minnesota Med. **28**:669, 1945.

3. Cytoplasm is abundant or scanty, basophilic, frequently vacuolated and rather foamy, especially in adenocarcinoma.

4. Cells possess hyperchromatic nuclei which vary in size.

5. Nucleoli (numbering 1 to 3) are prominent.

6. Numerous mitotic figures may sometimes be seen.

7. The cells usually occur in groups, nests or sheets, but many occur singly or in small groups, only two or three together; when the cells do occur in nests or sheets, of course, there is no question as to their identity; but when they appear in small numbers only, definite identification is more uncertain.

8. Metastatic cells appear undifferentiated and often resemble undifferentiated stem cells of the reticuloendothelial system.

To check this list of criteria as opportunity arose at autopsies or surgical biopsies, direct smears from cut surfaces of tumor nodules were made and stained by the technic described. The cytologic details agreed closely with those observed

TABLE 1.—*Distribution of Cases According to Type of Primary Cancer*

Carcinoma of breast	5
Carcinoma of stomach	4
Carcinoma of prostate	3
Carcinoma of bronchus	2
Multiple myeloma	2
Carcinoma of cervix	2
Osteogenic sarcoma	2
Carcinoma of large bowel	2
Carcinoma of kidney	2
Carcinoma of pancreas	1
Reticulum cell sarcoma	1
Primary site undiagnosed	6
Total	32

on the smears of bone marrow. From the experience gained in this work it may be said that the cytologic qualities as set forth here are the qualities of malignant cells in general when those cells are stained by a Romanowski technic.

SELECTION OF CASES

In this study patients who were known to have or were strongly suspected of having metastatic lesions were selected. No regard was given to the source of the primary tumor. Those which frequently metastasize to bone were not selectively chosen. An effort was made to collect as large a series as possible. In table 1 is shown the distribution of the 32 cases as to primary site. The patients were 12 women and 20 men. Two were in the third decade of life, 11 in the fifth, 8 in the sixth, 10 in the seventh and 1 in the eighth. A brief summary of the clinical history of each patient is appended to this article.

OBSERVATIONS

The appearance of the bone marrow of these patients varied considerably, but in most instances the marrow did not present a strictly normal distribution of one or more of the cell types, even when tumor cells were not found. In table 2 the distribution of cells and the findings in

the cases are summarized. Wintrobe figures are taken as the normal. In 8 of the 32 cases, cells possessing the criteria for malignancy, as set forth in a previous section, appeared in small groups, clumps or sheets permitting the unequivocal diagnosis of metastatic tumor. In 4

Fig. 1 (case 2).—Aspirated marrow, showing complete replacement of normal marrow with tumor tissue; × 220.

more cases scattered throughout various smears were single cells with similar appearance, suggesting the presence of metastatic tumor. I am unwilling, at present, to make an unequivocal diagnosis of cancer

TABLE 2.—*Summary of Cell*

Case No.	Diagnosis	Hematocrit, %	Red Blood Cells, Mill.	Hgb. Gm.	White Blood Cells, Thous.	Type of Marrow	Eos. Myel.	Eos.	Bas. Myel.	Bas.	Myeloblast	Promyelo.	Myel.	Meta.
1	Ca lung?	34	3.9	11.3	5.0	Cellular	6.5	0.0	0.0	0.5	0.0	1.5	2.0	2.0
2	Ca stomach	..	5.8	10.9	2.6	No normal marrow	...	...	...	...	...	...	...	...
3	Ca breast	..	...	....	...	Too little normal marrow	...	...	...	...	...	...	...	...
4a	Ca lung	..	4.4	14.0	13.0	Cellular	2.8	2.0	0.0	0.0	0.4	0.4	5.6	17.2
4b	Ca lung	..	...	....	...	Cellular	4.3	0.7	0.0	0.0	0.3	0.6	6.7	13.3
5	Ca bronchus	..	2.0	5.5	...	Poorly cellular	7.0	2.5	1.0	0.0	0.0	1.5	10.0	12.5
6	Multiple myeloma	45	...	14.4	10.2	Very cellular	...	...	...	...	...	...	...	...
7	Ca cervix	..	4.4	14.7	5.9	Cellular	2.0	0.8	0.0	0.0	0.4	0.8	10.4	18.8
8	Retroperitoneal sarcoma	31	3.9	11.5	10.8	Very cellular	5.5	3.5	0.0	0.0	1.0	4.0	19.0	19.0
9	Multiple myeloma or metastatic Ca	..	3.9	12.0	6.3	Poorly cellular	0.0	2.5	0.0	0.0	0.0	0.0	1.5	7.0
10	Ca stomach	..	...	....	...	Cellular	4.5	2.5	0.0	0.0	0.0	3.5	11.5	17.0
11	Ca prostate	34	...	....	...	Cellular	4.6	4.0	0.0	0.0	0.3	2.0	13.0	9.7
12	Osteogenic sarcoma	44	...	15.7	...	Cellular	3.2	0.4	0.8	0.0	0.8	2.0	8.0	16.8
13	Ca breast	..	...	....	...	Cellular	1.5	0.5	0.0	0.0	1.0	2.0	13.0	13.5
14	Ca primary (?)	..	2.7	7.4	9.6	Moderately cellular	3.2	0.4	0.8	0.4	0.4	2.4	15.6	20.0
15a	Ca breast	32	3.3	11.0	6.1	Very cellular	6.6	2.2	0.0	0.0	0.2	0.6	8.6	9.4
15b§	Ca breast	..	3.5	11.0	11.2	Very cellular	5.6	1.3	0.0	0.0	0.3	0.9	5.6	10.0
16	Ca colon	..	...	....	...	Very cellular	7.6	1.6	0.0	0.0	0.8	1.2	8.4	12.0
17	Ca pancreas	..	...	16.9	16.0	Cellular	0.0	1.5	0.5	0.0	0.5	0.5	16.5	9.0
18	Ca primary (?)	..	2.9	7.6	14.1	Cellular	2.0	0.8	0.0	0.0	0.4	1.2	16.4	18.4
19	Ca prostate	..	...	....	...	Moderately cellular	3.2	3.6	0.0	0.0	1.6	5.6	18.8	12.8
20	Ca cecum	15	2.3	3.5	...	Very cellular	4.0	1.5	0.0	0.0	0.5	0.5	9.0	5.0
21	Adenoca primary (?)	41	...	14.8	11.5	Moderately cellular	4.4	2.0	0.4	0.0	0.4	3.6	9.6	10.8
22	Adenoca kidney	30	4.3	9.4	14.5	Cellular	4.0	2.4	0.0	0.0	0.4	3.3	10.0	14.4
23	Ca breast	37	4.3	12.5	9.4	Cellular	5.0	3.5	0.0	0.0	0.5	2.5	35.5	12.0
24	Myeloma	35	3.8	11.8	...	Cellular	2.0	1.0	0.5	0.5	1.0	1.5	7.5	13.5
25	Osteogenic sarcoma	31	3.3	9.8	...	Very cellular	1.6	1.6	0.4	0.4	0.0	0.0	24.0	14.4
26	Ca stomach	26	3.6	8.0	...	Moderately cellular	1.2	1.6	0.0	0.0	0.8	2.0	7.2	13.6
27	Ca prostate	..	3.8	12.5	5.4	Very cellular	5.5	1.0	2.0	0.0	0.5	2.5	21.0	14.0
28	Ca primary (?)	20	1.9	6.2	Leukocytosis	Cellular	1.2	0.0	0.4	0.4	0.4	2.0	5.2	22.4
29	Ca cervix	..	2.9	9.5	6.7	Cellular	3.5	1.5	0.0	0.0	0.0	0.5	5.0	23.5
30	Ca stomach	34	3.4	11.3	8.4	Moderately cellular	4.0	1.2	0.0	0.0	0.8	2.0	8.0	21.2
31	Ca kidney	41	5.5	15.0	4.2	Very cellular	0.0	1.6	0.0	0.0	0.0	2.4	18.0	13.6
32	Ca breast	..	2.7	8.0	7.0	Cellular	0.8	0.4	0.0	0.0	0.4	2.4	2.4	26.4

* These cells were deeply basophilic, with abundant foamy cytoplasm and prominent nucleoli.
† These cells were characterized by dense chromatin, vacuolated cytoplasm and prominent nucleoli.
‡ These cells had deeply basophilic cytoplasm, a loosely clumped nucleus and large nucleoli.
§ Same case as 15a two months later.

Stab Forms	Seg.	Lymph.	Mono.	R-E	Plasma	Pro-eryth.	Erythd.	Normoblast Early	Normoblast Late	Mega.	M. F.	Abnormal Cells	Bone Metastases (X-Ray)
5.5	58.0	7.5	4.0	3.0	5.5	0.0	0.0	1.0	0.5	+	...	Several clumps of tumor cells; many plasma cells atypical	+
...	....	...	...	...	...	...	...	Absent		...	...	Sheets of tumor cells*	+
...	....	...	...	...	...	...	...	Absent		...	...	Similar to case 2	+
22.8	13.6	9.2	0.8	2.8	5.6	0.0	0.8	3.2	12.4	+	0.4	None	0
29.3	7.7	3.7	0.3	1.3	4.3	0.0	1.7	4.0	20.7	0.7	0.3	None	0
29.0	12.5	5.5	1.5	3.0	2.0	0.0	0.5	3.0	7.5	0.5	0.5	None	0
...	....	...	...	...	30-40%	...	...	...	...	...	...	Abnormal plasma cells in clumps, many with 2 nucleoli	0
22.4	4.8	8.8	0.4	2.8	3.6	0.0	0.8	5.2	18.0	+	...	One group of 4 cells together †	0
13.5	3.0	5.0	0.0	1.0	1.5	0.5	0.5	2.5	17.5	0.5	2.5	None	0
8.0	32.0	13.0	0.0	1.0	12.0	0.0	0.5	1.0	18.0	+	...	Many abnormal plasma cells; groups of larger cells ‡	+
22.0	9.0	5.0	0.0	3.0	10.5	0.0	0.0	0.5	6.5	1.5	...	Fields 10-12 plasma cells, 3% unclassified	+
14.3	3.7	9.7	0.0	1.3	2.7	0.0	1.0	6.3	25.3	0.7	1.3	None	+
21.6	9.2	5.2	0.4	1.2	3.6	0.8	0.8	7.2	16.0	1.6	0.4	None	0
8.0	2.5	14.0	0.0	2.0	2.5	1.0	1.0	6.5	29.5	+	1.5	Increase in plasma cells, many in groups of 5-8; no tumor cells	+
30.4	6.4	5.6	0.0	0.8	1.6	0.0	0.0	2.8	9.2	+	?	Occasional atypical cells	0
32.2	5.4	6.8	0.0	2.6	3.0	0.2	1.2	3.2	16.4	0.6	0.8	No tumor cells; megakaryocytes very plentiful	+
25.6	8.3	3.3	0.0	2.3	2.6	0.3	1.3	7.3	21.6	1.3	1.0	Nests of tumor cells (2) on 4 smears; megakaryocytes greatly increased	+
12.0	3.6	12.0	0.8	1.6	1.6	0.0	1.2	4.0	30.4	0.4	0.8	None	0
19.5	13.5	8.5	0.0	1.0	3.0	1.0	2.5	6.5	15.0	1.0	0.0	Scattered atypical cells; many megakaryocytes	+
23.2	6.8	2.0	0.0	1.2	3.8	0.4	1.2	3.2	13.6	+	0.4	None	+
18.0	4.8	4.0	0.4	2.8	4.8	0.0	0.4	2.0	17	+	...	None	+
15.0	2.5	3.0	0.0	3.5	4.5	1.0	3.0	7.5	37.5	0.5	1.5	Plasma cells in groups 4 to 6	0
18.8	8.4	12.0	0.4	3.6	0.8	0.4	0.8	4.4	18.0	0.4	0.8	None	+
30.0	4.0	2.4	0.0	0.8	3.2	0.0	0.4	2.8	21.2	+	1.2	Occasional atypical cell	+
12.0	3.0	8.0	0.5	1.5	6.0	0.0	0.0	1.5	8.0	+	0.5	None	+
16.0	8.0	13.0	0.0	1.5	7.5	1.5	1.0	5.0	21.5	+	0.0	Abnormal plasma cells, few with 2 to 3 nuclei	+
16.0	4.0	5.2	0.0	1.6	7.2	0.0	0.4	6.0	16.4	0.4	0.0	None	+
28.0	10.8	6.0	1.2	2.8	1.6	0.0	1.2	3.2	17.2	1.2	0.0	0.4% unclassified; stem cells?	0
9.5	10.0	2.0	2.0	1.0	3.5	0.0	0.0	5.0	20.0	Many	0.5	None	+
5.2	5.2	4.0	1.6	3.6	2.8	0.0	1.6	12.0	30.8	+	1.2	Groups of 3, 4, and 6 on 3 different slides; scattered single cells	0
34.5	14.0	3.5	0.0	2.0	0.5	0.0	0.0	2.0	8.0	1.0	0.5	None	0
26.8	6.4	10.0	0.0	1.2	0.4	0.4	0.4	4.0	12.8	+	0.4	None	0
14.0	6.4	6.0	0.4	7.2	12.4	0.0	0.0	0.8	6.8	0.4	1.6	8.4% unclassified, probably tumor cells; many plasma cells abnormal	?
9.6	2.4	2.8	0.0	0.8	0.8	0.0	2.8	8.4	38.4	0.4	0.4	None	

on the presence of single cells only, although I feel certain that such a declaration can probably be made as one gains more and more experience.

There were other unusual features brought out by these studies that seem at variance with what previous workers have reported. Nor-

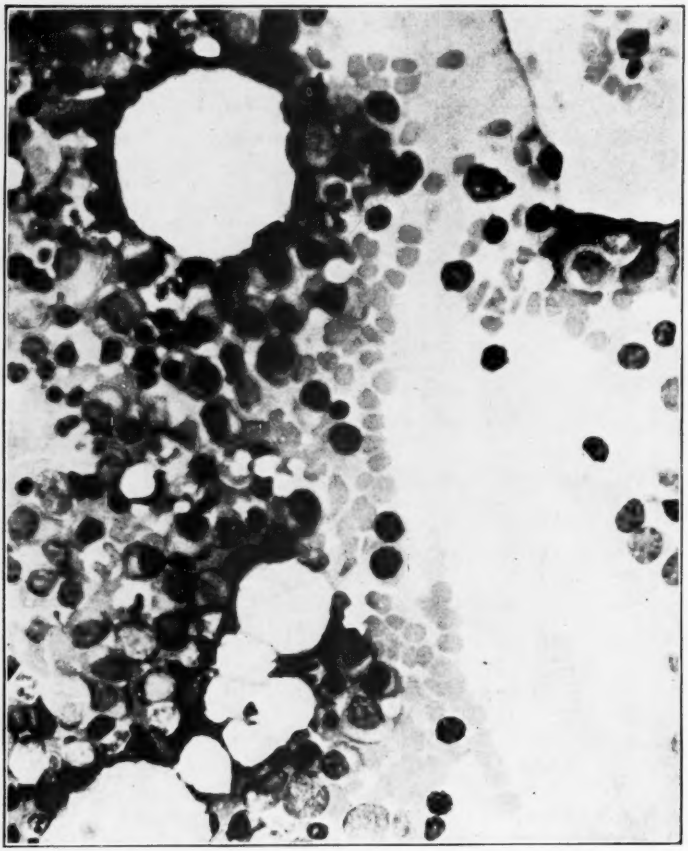

Fig. 2 (case 6).—Bone marrow showing a large percentage of abnormal plasma cells or myeloma cells; × 470.

densen distinctly pointed out that in the majority of his 17 patients with cancer eosinophilic cells were infrequent. Contrariwise, it is shown here that in nearly half (44 per cent) of the patients a distinct increase in eosinophilic elements appeared and the remainder showed a number

at least within normal limits. Most writers mention only briefly or make no point at all of the number and appearance of the reticuloendothelial cells and plasma cells. In this series one of the most striking and consistent findings was an increase in the number of plasma cells and reticuloendothelial cells. Twenty-one patients had an elevated number

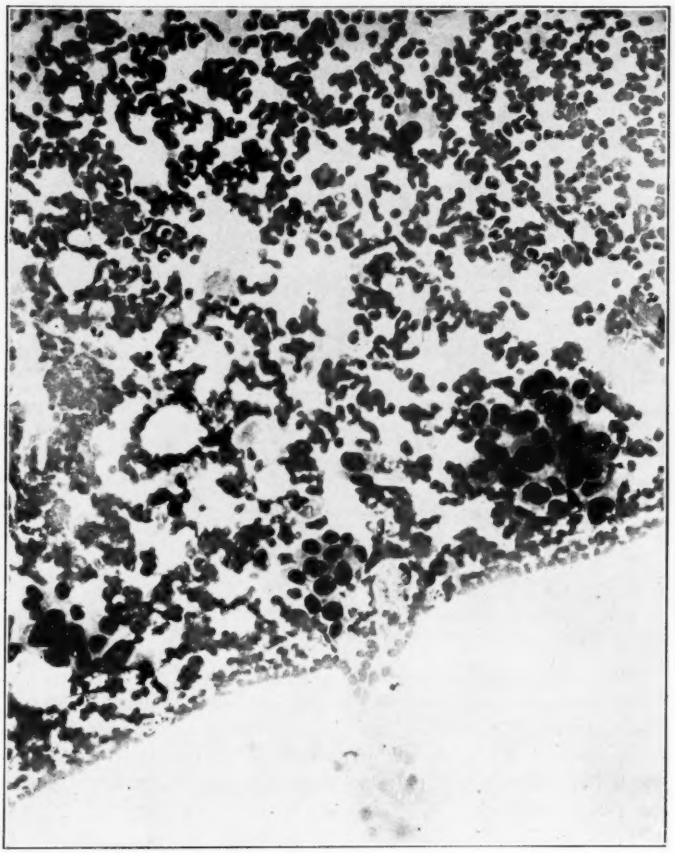

Fig. 3 (case 3).—Bone marrow showing several nests of tumor cells. Note also single tumor cells scattered through smear; × 220.

of plasma cells, and 12, an increase in reticuloendothelial cells. Not only the number but also the character of these cells was abnormal. In several of these cases the plasma cells occurred in large clumps, of 10 to 15; the typical "wheel spoke" clumping of the chromatin had

disappeared; the cytoplasm was foamier and often contained azurophilic granules. In 2 instances, cases 10 and 31, if one did not have clinical or autopsy information, a diagnosis of multiple myeloma would have been seriously entertained from the cytologic study alone. In case 31, the patient had a plasma globulin content of 5 Gm. and a uric acid content of 10 mg. to help support the case for myeloma; but, as noted in the protocol, autopsy revealed a massive renal carcinoma with widespread metastases. M. S. (case 10) had a large adenocarcinoma of the stomach with metastases to nearly every conceivable location.

TABLE 3.—*Summary of Chief Observations*

	Cases	
	Number	Percentage
Cases studied	32	100
Definitely positive bone marrow	8	25
Doubtfully positive bone marrow	4	12.5
Anemia	22	68.75
(Female: Hematocrit <35%, or <3, 900,000 red blood cells or <11.0 Gm. Hgb.)		
(Male: Hematocrit <40%, or <4, 200,000 red blood cells or <12.5 Gm. Hgb.)		
Leukocyte count above 10,000	8	25
Leukocyte count below 5,000	2	6.25
Leukocyte count 5,000 to 7,500	7	21.9
Leukocyte count 7,500 to 10,000	3	9.4
Plasma cells in bone marrow increased 2.5 per cent or more	22	68.75
Reticuloendothelial cells in bone marrow increased 2.5 per cent or more	12	37.5
Reticuloendothelial cells and plasma cells both increased	8	25
Eosinophilic cells increased	15	46.9
(Myelocytes 4 per cent or more, older cells 4 per cent or more, combined 7 per cent)		
Cellular to very cellular bone marrow	25	78.1
Poorly cellular bone marrow	2	6.25
Erythroid elements decreased 8 per cent or less	5	18.75
Megakaryocytes notably increased	4	12.5
One or more abnormalities of the bone marrow	28	87.5

Almost all the patients showed a very cellular marrow; in only 2 was it poorly cellular, and in only 3 were the erythroid elements depressed below the lower limits of normal despite the fact that over half the patients had anemia. In a few patients, Mrs. F. H. (case 15) being an outstanding example, the number of megakaryocytes in the bone marrow was notably increased.

Table 3 presents a summary of the significant findings in the series.

COMMENT

It would appear from the cited observations that it is possible in a fair percentage of cases actually to observe malignant cells in sternal marrow obtained by routine aspiration and stained with ordinary blood stains.

Clinically the finding of tumor cells testifies to the lateness of the process. It is not inconceivable, however, that the sternal marrow may actually be the first clue to the nature of the disease process going on in the patient, and it therefore behooves the examiner to search diligently

Fig. 4 (case 3).—High power magnification of one of clumps seen in figure 3. Note variation in size and shape of cells, hyperchromatic nuclei, nucleoli and foamy cytoplasm; × 470.

a number of smears and not be content with looking at one or two and counting 200 cells.

Previous to this work, it had been my conception that when plasma cells were increased to 8 to 10 per cent and showed changes in their cytologic characteristics the diagnosis of myeloma was to be considered

first. It would appear from the findings in this series of cases that such changes can occur in persons with certain chronic diseases such as carcinoma, and these results serve to emphasize again the importance of basing a diagnosis on the entire picture and not on just one feature.

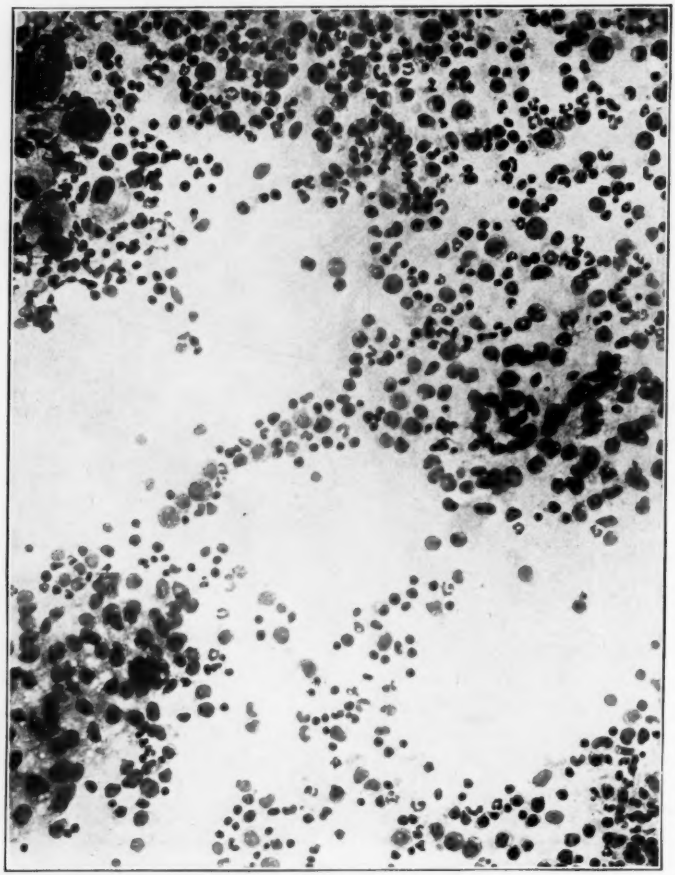

Fig. 5 (case 15b).—Bone marrow. These clumps of tumor cells were the only clumps found on the entire smear. A megakaryocyte may be seen in upper left corner; × 220.

The finding of an increased number of eosinophilic cells in the bone marrow in the absence of other known causes for eosinophilia such as dermatitis, asthma or other allergic states, the presence of an increase in plasma cells and/or reticuloendothelial cells, the presence of single

atypical cells of undifferentiated character—any one or all of these should suggest the presence of a malignant tumor which has metastasized, and one may direct one's further efforts toward finding the primary site.

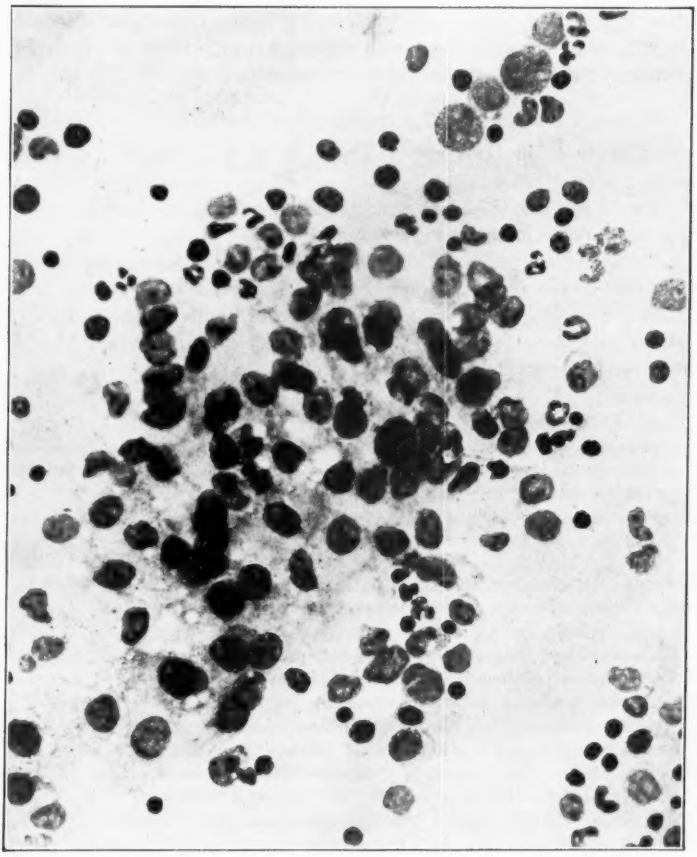

Fig. 6 (case 15b).—High power magnification of one of tumor cell groups in figure 5. Foaminess of cytoplasm and nucleoli are especially well shown here. The tumor cells may be contrasted with normal myeloid cells shown in the upper right corner; × 470.

It should be pointed out again and reemphasized that unless the tumor cells occur in clumps and groups one cannot categorically make a definite diagnosis of metastases, but certainly the suggestive findings as

given could be valuable clues and aid in the further investigation of the patient.

Most explanations for the anemia in patients with a malignant tumor have been based on the premise that the tumor cells have crowded out the normal erythroid elements. The figures cited in tables 2 and 3 raise the question again as to whether that is the answer, for it would appear that even in patients with anemia the percentage of erythroid elements in the bone marrow is within normal range.

SUMMARY

A study of the bone marrow picture in 32 patients with metastatic cancer is reported.

In 28 patients (87.5 per cent) there were deviations from accepted normal patterns in one or more respects.

While actual tumor cells could be identified in the marrow of 25 per cent of the patients, other abnormal features were observed in a large percentage of preparations. Increase in number of plasma cells, reticuloendothelial cells, and/or eosinophilic elements certainly should suggest the presence of metastases.

PROTOCOLS OF CASES

CASE 1.—Mrs. F. K., a 44 year old Chinese woman had had a tumor the primary site of which was not definitely determined; it was thought to be a lung. Permission for autopsy was refused. Roentgenograms provided evidence of destruction of the twelfth rib and the transverse process of the first lumbar vertebra on the left.

CASE 2.—Miss E. T., a 49 year old white woman, had undergone partial gastric resection for adenocarcinoma five years previously. There was roentgen evidence of widespread metastases to the pubis, spine, pelvis and femurs.

CASE 3.—Mrs. M. L., a 41 year old white woman, gave a history of removal of the right breast for carcinoma two years previously and recurrence in supraclavicular nodes. Pathologic fracture of the right femur occurred, with roentgen evidence of metastases at the site of fracture.

CASE 4.—Mr. A. E., a 57 year old white man, had an adenocarcinoma of the left main stem bronchus diagnosed by roentgenograms and bronchoscopy with biopsy. It was thought to have metastatized because massive pleural effusions developed, but roentgenograms showed no evidence of metastases.

CASE 5.—Mr. E. L., a 49 year old white man, gave a history of grade 4 hemangioepithelioma which had been irradiated, with complete remission eleven years before. Roentgenograms showed opacity in the left upper pulmonary field, enlarged hilar nodes on the left and opacity in the stomach. Biopsy of a nodule in the neck was reported as showing anaplastic squamous cell carcinoma. At autopsy it was the pathologist's opinion that the primary site was probably a bronchus. There was no evidence of recurrence of the hemangioepithelioma.

CASE 6.—Mr. S. R., a 58 year old man presented roentgen evidence of destruction of the body of the second cervical vertebra at the site of an old fracture. After sternal aspiration a diagnosis of multiple myeloma was made. Since that time, further lesions demonstrable roentgenologically have developed.

CASE 7.—Mrs. L. H., a 48 year old woman, gave a history of grade 3 squamous cell carcinoma of the cervix, diagnosed by biopsy and treated with roentgen rays and radium. Jaundice, anorexia and nausea developed. A roentgenogram revealed extrinsic compression of the duodenum and an enlarged liver.

CASE 8.—Mr. H. P., a 55 year old man, had a diagnosis of retroperitoneal reticulum cell sarcoma made by exploration and biopsy at operation. There was no roentgen evidence of metastases.

CASE 9.—Mr. P. M., a 60 year old man, presented roentgen evidence of destructive lesions of the fourth thoracic vertebra and neurologic changes resulting from block demonstrated by operation at the level of the second thoracic vertebra. No satisfactory pathologic diagnosis was obtained. Roentgenograms showed some areas of decreased densities. A questionable diagnosis of multiple myeloma or metastatic carcinoma was made. Permission for autopsy was refused.

CASE 10.—Mr. M. S., a 45 year old man, had adenocarcinoma of the stomach demonstrated roentgenologically and proved by exploration and operation. There was roentgen evidence of metastases to the spine.

CASE 11.—Mr. A. P., a 60 year old man, gave a history of prostatic carcinoma of one and one-half years' duration. Roentgenograms gave evidence of an osteolytic process in the eleventh thoracic vertebra. Orchiectomy had been performed three days before sternal aspiration.

CASE 12.—Mr. D. D., a 48 year old man, had an osteogenic sarcoma of the right tibia proved by biopsy and examination at amputation. There was no roentgen evidence of metastases. Sternal aspiration was done two days after amputation.

CASE 13.—Mrs. R. K., a 26 year old woman with history of carcinoma of breast of one and one-half years' duration, had roentgen evidence of metastases to the spine and clinical evidence of possible metastases to the brain. Autopsy was not performed.

CASE 14.—Mr. R. F., a 64 year old man, had a diagnosis of adenocarcinoma made from biopsy of a supraclavicular node, and tumor cells were found in ascitic fluid. There were physical signs and roentgen evidence of a pathologic process in the right lower pulmonary field. The primary site was not proved.

CASE 15.—Mrs. F. H., a 64 year old woman with diagnosis of adenocarcinoma of the breast, had undergone radical mastectomy six and one-half years previously. There was roentgen evidence of metastases to the spine, ribs, femurs and sacrum.

CASE 16.—Mr. F. H., a 57 year old man, had carcinoma of the colon diagnosed by roentgenograms and proved by exploration and biopsy. The liver and spleen were enlarged, but there was no roentgen evidence of other metastases.

CASE 17.—Mr. W. M., a 52 year old white man, had a diagnosis of squamous cell carcinoma made by biopsy of a lymph node in the right axilla. Block at the level of the fifth thoracic vertebra and jaundice developed. Autopsy showed anaplastic carcinoma of the pancreas with multiple massive metastases to lymph nodes, liver, spleen, spine and ribs.

CASE 18.—Mr. T. M. was a 61 year old man with a mass in the left lumbar region, enlarged liver and spleen, osteolytic lesions in the left ilium, and an acid phosphatase level of 8 Armstrong units. Anaplastic carcinoma was diagnosed by biopsy of the ilium. The primary site was not diagnosed.

CASE 19.—Mr. S., a 65 year old man, had carcinoma of the prostate gland with roentgen evidence of metastases to the spine and pelvis.

CASE 20.—Mrs. A. A., a 67 year old woman, with a diagnosis of adenocarcinoma of the cecum proved by exploration and biopsy, had no roentgen evidence of

metastases, but at operation it was noted that the tumor had extended to include the bladder and nodes removed.

CASE 21.—Mr. E. C., a 50 year old man, had an anaplastic carcinoma diagnosed by exploratory laminectomy. The primary site had not yet been discovered.

CASE 22.—Mr. J. A., a 50 year old man with adenocarcinoma of the left kidney, diagnosed by pyelography and biopsy of a metastatic tumor mass in the left femur, had roentgen evidence of metastases to ribs. The liver was enlarged.

CASE 23.—Miss O. R., 55 years old, had carcinoma of the breast, first noted six years previously. The diagnosis was proved by biopsy, and roentgen treatment was given. There was roentgen evidence of metastases to the pelvis, skull and spine.

CASE 24.—Mrs. A. R., a 48 year old woman, had a distinctive lesion of the body of the seventh thoracic vertebra. After sternal aspiration the diagnosis of multiple myeloma was made. Additional lesions appeared, and Bence Jones protein was present for first time four months after the original diagnosis.

CASE 25.—Mr. S. d'A., a 22 year old man with osteogenic sarcoma of the right femur, proved by biopsy, had roentgen evidence of widespread metastases to the lungs, skull and left femur.

CASE 26.—Mr. J. L., a 55 year old man, had a history of massive gastrointestinal hemorrhage. Roentgenograms revealed deformity of a large portion of the body of the stomach and the fundus. The patient was not operated on and did not die in the hospital. There was no roentgen evidence of other metastases.

CASE 27.—Mr. W. S., a 65 year old man, had a presumptive diagnosis of adenocarcinoma of the prostate gland. Osteoplastic lesions of the body and wings of the sacrum were demonstrated two and one-half years before. Cord bladder developed. Recent roentgenograms gave evidence of extension of the lesions in the pelvis. Orchiectomy produced clinical improvement.

Case 28.—Mr. N. F., a 48 year old man, had severe gradually developing macrocytic anemia and gastrointestinal symptoms of relatively short duration. The primary site was not determined, whether stomach or pancreas.

CASE 29.—Mrs. E. B., a 49 year old woman with carcinoma of the cervix diagnosed by biopsy two years before, had been treated with roentgen rays. There was no roentgenologic evidence of metastases, but anemia, pain in the lumbar area and neurologic symptoms in the lower extremities developed—all clinical symptoms of metastases by extension.

CASE 30.—Mr. F. Ha., a 58 year old man, had had a carcinoma of the stomach removed two years ago. Although there was no roentgen evidence of metastases, there was clinical evidence of marked anorexia, weight loss and abdominal pain. The patient died. Autopsy confirmed the presence of widespread metastases.

CASE 31.—Mrs. H. C., a 68 year old woman, gave a history of "feeling sick" for three months and of rapid appearance of masses in the neck and left side of the abdomen. Autopsy disclosed a massive tumor apparently primary in the left kidney with widespread metastases throughout the body.

CASE 32.—Mrs. J. S., a 76 year old woman, gave a history of radical mastectomy (excision of the right breast) for adenocarcinoma three years previously. Anemia was noted in March, three months before her admission.

Dr. Robert S. Evans gave advice in the performance of this study. Miss Rose T. Duane gave technical assistance. Physicians of the staff of Stanford University Hospitals and the United States Marine Hospital, San Francisco, made cases available for this study.

633 North Forest Avenue, Webster Groves 19, Mo.

MOTOR MANIFESTATIONS OF HERPES ZOSTER

Report of a Case of Associated Permanent Paralysis of the Phrenic Nerve

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HERPES zoster is a nervous disorder which is usually associated with dermatologic manifestations. It was the latter which gave the disease its name, since its external manifestations were known to the ancients. Herpes is a generic term which has been applied to numerous dissimilar acute inflammatory reactions of the skin and, as such, is misleading. We shall omit it during the rest of the present paper and shall refer to the disease entity under discussion as zoster. This latter term comes from the Greek ζωστήρ and refers to the fact that the disease when leading to dermatologic manifestations on the trunk spreads around it like a girdle. Though zoster is not an accurate term, the disease denoted is evident; therefore, this nomenclature is utilized in the present report.

That zoster is a nervous disorder was established by pathologic examination in 1862.[1] Its neuropathology was established on a firm foundation in 1900 by Head and Campbell.[2] Motor phenomena as a manifestation of the process were described in 1866.[3] That the anterior horn was probably frequently involved even though no external paralysis was present was not made evident until 1924,[4] but the fact has been verified since that time.[5] That the disease is of viral origin has been

1. von Bärensprung, F. G. F.: Fernere Beiträge zur Kenntnis des Zoster, Ann. d. Char.-Krankenh. zu Berlin **10**:37, 1862.

2. Head, H., and Campbell, A. W.: The Pathology of Herpes Zoster and Its Bearing on Sensory Localization, Brain **23**:353, 1900.

3. Broadbent, W. H.: Case of Herpetic Eruption in the Course of Branches of the Brachial Plexus Followed by Partial Paralysis in Corresponding Motor Nerves, Brit. M. J. **2**:460, 1866.

4. Lhermitte, J., and Nicolas, M.: Les lésions spinales du zona: La myélite zostérienne, Rev. neurol. **31**:361, 1924.

5. (*a*) Denny-Brown, D.; Adams, R. D., and Fitzgerald, P. J.: Pathologic Features of Herpes Zoster: A Note on "Geniculate Herpes," Arch. Neurol. & Psychiat. **51**:216 (March) 1944. (*b*) Adams, R. D.: The Pathological Features of Herpes Zoster, Bull. New England M. Center **6**:12, 1944. (*c*) Riggs, H. E., and Rupp, C.: Pathological Changes in Early Herpes Zoster, J. Neuropath. & Exper. Neurol. **7**:100, 1948.

conclusively established, the organism probably being closely related to, though not identical with, the virus of varicella.[6] On reaching the nervous system, probably as an ascending myelitis, the virus causes diffuse damage, as noted later in this report. It usually attacks one or two segments, most vigorously destroying the posterior ganglion on that level, and travels down to the skin to cause the characteristic eruption.[7] According to the extent of damage in the different areas of the nervous tract, other manifestations become apparent. These have formerly been referred to in the literature as "complications," but they should not be called such, since they are part and parcel of the disease process, just as paralysis is an integral part of the manifestations of acute anterior poliomyelitis. This paper is concerned only with the motor manifestations of the essentially neurologic disorder zoster. A manifestation heretofore not reported is also presented and discussed.

MOTOR SYMPTOMS

Though the latest textbooks of medicine, dermatology and neurology, as well as recent reviews,[8] refer to motor symptoms as a rare complication, in 1916 Weber[9] had already noted that there was "a large literature in regard to herpes zoster associated with muscular paresis and muscular atrophy." He described a case with paralysis of the arm and 1 with oculomotor paresis and paralytic mydriasis. Lesions of the upper motor neuron are usually due to lesions in the brain. The former are rare, may present as a hemiplegia and are often fatal. Lower motor neuron pareses are relatively common and may involve either the cranial or the spinal nerves. They are almost always associated with a herpetic eruption, but zoster paresis without dermatologic manifestations has been reported.[10]

Oculomotor paresis is common and is usually associated with zoster ophthalmicus, but not invariably so. There may be a single muscle involved, or all the muscles supplied by the third, fourth and sixth cranial nerves may be paretic. Of 2,250 cases of ophthalmic zoster

6. Stokes, J., Jr.: Varicella–Herpes Zoster Group, in Rivers, T. M.: Viral and Rickettsial Infections of Man, Philadelphia, J. B. Lippincott Company, 1948, chap. 23, p. 395.

7. Stern, E. S.: Mechanism of Herpes Zoster and Its Relationship to Chicken-Pox, Brit. J. Dermat. **49**:263, 1937. Montgomery, D. W.: Herpes Zoster as a Primary Ascending Neuritis, Arch. Dermat. & Syph. **4**:812 (Dec.) 1921.

8. Baird, P. C., Jr.: Herpes Zoster, New England J. Med. **228**:568, 1943.

9. Weber, F. P.: Herpes Zoster: Its Occasional Association with a Generalized Eruption and Its Occasional Connection with Muscular Paralysis, Internat. Clin. **3**:185, 1916.

10. (*a*) Aitken, R. S., and Brain, R. T.: Facial Palsy and Infection with Zoster Virus, Lancet **1**:19, 1933. (*b*) Spillane, J. D.: Bell's Palsy and Herpes Zoster, Brit. M. J. **1**:236, 1941.

recorded by Edgerton up to 1942, ocular muscles were involved in 13 per cent.[11] The third nerve is most frequently involved, there being partial or total ptosis or mydriasis. Abducens paralyses occur less frequently, and isolated paralysis of the trochlear nerve is the least common. A combination of paralyses of any two ocular nerves may be present; there are recorded 40 cases of simultaneous paralysis of the third, fourth and sixth nerves. There are only 2 cases of bilateral paralysis recorded in the literature, one of bilateral paralysis of the third nerve and one of bilateral paralysis of the sixth nerve.[12] The paresis most often occurs after the eruption and is transient, lasting up to several months. It may be permanent. The production of a nuclear lesion is probably due to extension of the virus infection, either to the motor nerve or to the neuraxis.

Facial palsy is perhaps the commonest of the motor lesions. Until recently it was thought, because of the work of Hunt,[13] who originally described the syndrome of facial palsy with zoster, that the geniculate ganglion was always involved. The facial nerve was also involved in 7 per cent of cases of ophthalmic zoster and in certain cases of cervical zoster. It was felt that in those cases in which there were no cutaneous lesions in the seventh nerve distribution the ganglion cells were sufficiently involved to have produced paresis without herpes. This concept has been disproved by the work of Denny-Brown and his associates [5a] and by that of O'Neill.[14] The former showed pathologically that lesions of the geniculate ganglion do not necessarily accompany the facial palsy. In many of O'Neill's cases there was no herpes or other evidence of involvement of the geniculate ganglion but there was clearcut involvement of one or several other cranial ganglions or cervical segments. In these instances the infection involves the nerve or motor nuclei but the sensory apparatus remains unaffected. Like other types of motor paresis associated with zoster, facial palsy usually is transient, lasting weeks to months, but may be permanent.

Motor paralysis of spinal root distribution has been reported less commonly; reasons for this will be discussed later in this report. Broad-

11. Edgerton, A. E.: Herpes Zoster Ophthalmicus: Report of Cases and a Review of the Literature, Tr. Am. Ophth. Soc. **40**:390, 1942.

12. de River (1925) and Gallois (1924), cited by Edgerton.[11]

13. Hunt, J. R.: Herpetic Inflammations of the Geniculate Ganglion: A New Syndrome and Its Complications, J. Nerv. & Ment. Dis. **34**:73, 1907; Arch. Otol. **36**:371, 1907; Further Contributions to the Herpetic Inflammations of the Geniculate Ganglion, Am. J. M. Sc. **136**:226, 1908; Herpetic Inflammations: The Symptom-Complex of Acute Posterior Poliomyelitis of the Geniculate, Auditory, Glossopharyngeal and Pneumogastric Ganglia, Arch. Int. Med. **5**:631 (June) 1910.

14. O'Neill, H.: Herpes Zoster Auris ("Geniculate Ganglionitis"), Arch. Otolaryng. **42**:309 (Nov.-Dec.) 1945.

bent [8] first discussed this feature in 1866 when he reported a case of zoster of the arm and neck in which paralysis of the corresponding motor nerves of the brachial plexus developed. The subject was discussed by Carter and Dunlop [15] and by Taterka and O'Sullivan.[16] The latter reported 44 cases, including the 2 of Carter and Dunlop. There were 20 cases of paralysis of the upper extremity, 18 of paralysis of the muscles of the trunk and 6 of paralysis of the lower extremities. Since then, cases have been reported by Abercrombie,[17] Gordon and Tucker,[18] Parkinson,[19] Michaux, Granier and Lacourbe,[20] Lemmon [21] and Rosow.[22] Brain's case of pseudodiaphragmatic hernia [23] should also be included. In Abercrombie's case there was paralysis of the anterior tibial muscles corresponding to lesions of the fourth and fifth lumbar segments, whereas sensory changes in the leg and foot corresponded to the first and second sacral segments and the dermatologic reaction to the third sacral segment, thus showing diffuse motor and sensory involvement of the lower lumbar and the upper sacral segments. In the first case of Gordon and Tucker, there was muscular weakness and cutaneous involvement of the second and third lumbar segments in addition to facial involvement; in their second case, there was right hemiplegia. Parkinson's case showed both rash and paralysis in the distribution of the fifth cervical segment. Michaux's case involved the brachial plexus; in Lemmon's there were weakness and atrophy of the muscles supplied by the fifth and sixth cervical segments and in Rosow's case paralysis of the right deltoid muscle, paresis of the muscles of the right upper arm and forearm, slight weakness of the trapezius muscle and atrophy of the supraspinatus muscle and the thenar eminence. Our unusual case is described in detail in this paper.

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15. Carter, A. B., and Dunlop, J. B. W.: Paresis Following Herpes Zoster: A Report of Two Cases, Brit. M. J. **1**:234, 1941.

16. Taterka, J. H., and O'Sullivan, M. E.: Motor Complications of Herpes Zoster, J. A. M. A. **122**:737 (July 10) 1943.

17. Abercrombie, R. G.: Herpes Zoster with Muscular Paralysis and Disturbance of Sensation, Brit. M. J. **1**:778, 1941.

18. Gordon, I., and Tucker, J. F.: Lesions of the Central Nervous System in Herpes Zoster, J. Neurol., Neurosurg. & Psychiat. **8**:40, 1945.

19. Parkinson, T.: Rarer Manifestations of Herpes Zoster, Brit. M. J. **1**:8, 1948.

20. Michaux, L.; Granier, and Lacourbe, R.: Paralysie postzostérienne à type radiculaire supérieur du plexus brachial, Rev. neurol. **75**:154, 1943.

21. Lemmon, G. B., Jr.: Herpes Zoster with Motor Involvement: Report of a Case, U. S. Nav. M. Bull. **43**:357, 1944.

22. Rosow, H. M.: Herpes Zoster with a Motor Complication, M. Bull. Vet. Admin. **20**:350, 1944.

23. Brain, W. R.: Diseases of the Nervous System, ed. 2, New York, Oxford University Press, 1940, p. 465.

These cases of motor paresis have no particular pattern. In about 75 per cent of cases the eruption appears a few days to a few weeks before the paralysis, and in most of the remainder the paresis appears prior to the eruption, though at times the appearance of the symptoms is simultaneous. The percentage of cases without eruption is probably small but is indeterminate. To find the exact number, in every case of facial palsy, of oculomotor paresis or of other muscular paresis of unknown origin a lumbar puncture should be performed and complement fixation studies made. This probably should be done in all cases of these conditions which are associated with neuralgias. The motor lesions are invariably on the same side as the cutaneous and neuralgic manifestations, but in about one fifth of the cases the segments do not correspond. The paralysis may be permanent; there may be partial recovery or there may be complete recovery, depending on the severity and irreversibility of the damage to the anterior horn cells, the cranial nuclei or the nerve fibers involved.

PATHOLOGY

Von Bärensprung [1] first described the inflammatory changes in the dorsal root ganglion and in related portions of the spinal nerve. Head and Campbell [2] also demonstrated the lesions of the affected ganglion. They showed patchy inflammation of the neighboring ganglion and nerves, including the motor nerve root, and stated the belief that changes in the posterior roots and horns were secondary and degenerative. The papers of the French school of Lhermitte and his various collaborators [24] indicated more diffuse involvement. The patient of Lhermitte and Nicolas [4] died seven weeks after an acute attack of zoster. Pathologic examination of the spinal cord showed marked evidence of inflammatory changes in the anterior horns. In this case, as in most of the others noted in the remainder of this section, there was no record of a motor lesion clinically. Wohlwill [25] also noted extensive inflammatory changes in the central nervous system. Denny-Brown and others [5a] and Adams [5b] reported on 3 cases in which death occurred, due to various causes, within a few days to a few weeks after an attack of herpes. They observed, in addition to ganglionitis marked by pannecrosis of all or part of the ganglion, poliomyelitis involving both the anterior and the posterior horns and roots, relatively mild localized leptomeningitis and

24. Lhermitte and Nicolas.[4] Lhermitte, J., and Vermès: Les lésions du système nerveux central dans le zona, Rev. neurol. **1**:1231, 1930. Faure-Beaulieu, M., and Lhermitte, J.: Les lésions médullaires du zona idiopathique: La myélite zostérienne, ibid. **1**:1250, 1929.

25. Wohlwill, F.: Zur pathologischen Anatomie des Nervensystems beim Herpes Zoster, Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:171, 1924.

true peripheral mononeuritis in the nerves distal to the ganglion and in the anterior nerve root. The characteristic histopathologic picture of neurotropic virus infections was seen. The patient of Riggs and Rupp,[5e] who died suddenly on the third day of the disease from peripheral vascular collapse twenty minutes after the administration of a paravertebral block with procaine hydrochloride (novocain®) also showed diffuse involvement of the spinal cord. The almost constant finding of a moderate increase in cells in the cerebrospinal fluid in cases of zoster and the frequent occurrence of a slight excess of protein are also indicative of involvement of the cord. In addition to involvement of the meninges, the brain stem and the cortical tissue proper have been found to be affected in a number of cases.

CORRELATION OF PATHOLOGIC AND CLINICAL PICTURES

The variegated clinical pattern manifested in zoster is easily comprehended if one takes a quantitative point of view regarding the pathologic changes. The severity of the lesion in various locations determines the symptomatology. What factors decide the special localization and distribution of the lesions has not been determined. The facts that some patients show no paresis even though involvement of the anterior horns is present and that the paresis may be transient or permanent raise the questions of the extent of the lesion necessary to produce paresis and of the basis of the temporary nature of the palsy in a large percentage of cases. The answer seems to be that not all the anterior horn cells are necessary for apparently normal function. This has been shown experimentally in monkeys [26] and is clear from the cases described previously and from the extensive work in anterior poliomyelitis.[27] Since in the majority of cases only one or two segments are primarily and extensively involved, the segmental distribution may be such that the major innervation of a given muscle is not affected; also, certain muscles are supplied by more than one nerve. It is possible, since many muscles are members of a group functioning as a unit, that dysfunction of one muscle may go unrecognized unless specific tests of its condition are made. This is especially true in zoster, in which the dramatic dermatologic and neuralgic manifestations usually lead the patient to a dermatologist or a general practitioner. These physicians are preoccupied

26. Sabin, A. B., and Ward, R.: Nature of Non-Paralytic and Transitory Paralytic Poliomyelitis in Rhesus Monkey Innoculated with Human Virus, J. Exper. Med. **73**:757, 1941.

27. Bodian, D., and Howe, H. A.: Pathology of Early Arrested and Non-paralytic Poliomyelitis, Bull. Johns Hopkins Hosp. **69**:135, 1941. Sabin, A. B.: Pathology and Pathogenesis of Human Poliomyelitis, J. A. M. A. **120**:506 (Oct. 7) 1942.

with the cutaneous and sensory manifestations, and only a frank paresis is usually noted, transient minor motor symptoms or those involving the cord going unobserved. The damage to the neurons or motor fibers is undoubtedly reversible in most instances, as with other virus diseases.

One of us (S. L. H.) had occasion recently to see a patient who had had zoster involving apparently the fourth and fifth cervical segments. He stated that he had had some weakness of the arm during the period of the illness. When he was seen, there was no evidence of motor involvement or of other neurologic disturbance. Whether this case represented true paresis is a matter of conjecture at the time of this report since no neurologic tests of any nature were performed at the time of the symptoms, the weakness, when mentioned, having been casually attributed to the neuralgia by the attending physician, though the patient stated that the disappearance of the neuralgia antedated by a few days the recovery of full strength in the arm.

REPORT OF CASE

The following case, in which permanent paralysis of the phrenic nerve occurred with zoster, is reported in detail since it has no parallel in the literature.

W. H., a white man of 53, was in excellent health until June 1947. He had lived in Massachusetts all his life, had never had chickenpox or other childhood diseases, had never been vaccinated or received any immunizations and had had no operations or venereal disease. The patient had had no illnesses that year, nor had he a history of exposure to zoster or varicella. Ten days after his acting as a blood donor, the right arm having been used, an excrutiatingly painful vesicular eruption began to develop. This blossomed out as a typical zoster involving the third and fourth cervical segments on the right side. It was associated with regional lymphadenopathy. Three days after the eruption reached its maximum shortness of breath developed. This was not associated with cough or pain in the chest. The patient could breathe with greater facility when lying on his right side. A general physical examination was reported as noncontributory. The patient received symptomatic treatment for his eruption; ointments were applied locally and penicillin was given intramuscularly. After ten to fourteen days the eruption began to dry up, and it eventually cleared, except for some residual scars. However, exertional dyspnea persisted. The patient was treated variously for a neurasthenic disorder and for potential cardiac disease, receiving sedatives. On June 8, 1948 he was seen by one of us (A. H. C.). The patient was well developed. He had no palpitation, sweating, dizziness or other symptoms of neurasthenia. His only complaint was of dyspnea, especially on exertion but also after meals and on bending over. A diagnosis of paralysis of the right side of the diaphragm was made. Complete examinations (by S. L. H.) at that time and almost eleven months later, on March 20, 1949, revealed essentially the same physical findings. These consisted of scars in the region of the third and fourth cervical dermatomes on the right side, a slightly raised right side of the diaphragm which failed to descend on deep inspiration and a positive Hoover sign. Examination of the heart, lungs, abdomen, extremities and general nervous system was

noncontributory. Fluoroscopic examination revealed paralysis of the diaphragm on the right side. It behaved paradoxically, rising on inspiration and descending on expiration (the Kienböck phenomenon), this being noted especially on sniffing. There was no evidence on roentgenologic or fluoroscopic examination on either occasion of any pathologic features in the heart or lungs, and no masses were visible in the roots of the lungs or in the paramediastinal structures. There was no evidence of destruction of bone in the cervical portion of the spine, of narrowed intervertebral disk spaces or of abnormal articular facets. The roentgen appearance of the soft tissue of the cervical portion of the spine was normal. A gastrointestinal work-up revealed no paralysis of the swallowing reflex, no evidence of compression, dilatation or other abnormalities in the esophagus or in the remainder of the gastrointestinal tract and no signs of hiatus hernia. Electrocardiograms were within normal limits, as was the basal metabolic rate. The complete blood count and the blood sugar and nonprotein nitrogen revealed no abnormalities. The urinalysis was noncontributory. The vital capacity and the maximum breathing capacity were diminished. The ventilation equivalent for oxygen was normal.

The diagnosis was therefore made of exertional dyspnea due to paralysis of the diaphragm secondary to paralysis of the phrenic nerve associated with zoster. This diagnosis was justified by the concomitant onset of the two processes, the association of spinal segments in the two conditions and the failure to find any other cause for paralysis of the phrenic nerve and the diaphragm or for symptomatic dyspnea. There was no improvement in the patient's condition during the time of observation. Since the paralysis was of almost two years' duration at the time of writing, it is felt that it can be classified in the permanent category.

COMMENT

The phrenic nerve is the chief and probably the only motor nerve for the diaphragm.[28] It arises from the third and fourth cervical segments and also receives fibers from the fifth cervical segment. Its paralysis leads to diaphragmatic paralysis. Thus, disturbances of respiration can result from lesions in the third to fifth cervical segments, which involve the anterior horn cells of the phrenic nerve.[29]

Paralysis of the phrenic nerve resulting in paralysis of a hemidiaphragm is not infrequent. It may be caused by disease processes which involve the cervical portion of the cord (such as poliomyelitis), by neuritis from diphtheria or lead poisoning or by injuries to the cervical portion of the cord or to the phrenic nerve and by tumors in the mediastinum or the region of the neck, by an aneurysm of the aorta or by matted lymph nodes in the mediastinum, all of which can injure the phrenic nerve by compression. The paralyzed diaphragm subsequently thins out

28. Schlaepfer, K.: The Phrenic as the Nerve of Motor Innervation of the Diaphragm, Bull. Johns Hopkins Hosp. **34**:195, 1923.

29. Bing, R.: Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord, translated and edited by W. Haymaker, ed. 11, St. Louis, C. V. Mosby Company, 1940.

and becomes fibrous. Its failure to function in respiration causes an impairment of the ventilatory mechanism of the lungs and so may lead to dyspnea, especially on exertion. Tests for pulmonary function in the present case confirmed the presence of this process as the cause of the exertional dyspnea. It is interesting to note the shortness of breath after eating a full meal and on bending over. Each of these activities served to fix the left side of the diaphragm, thus causing further limitation of the vital capacity, which was already restricted by paralysis of the right side of the diaphragm.

Paralysis of the phrenic nerve as a motor manifestation of zoster has not previously been reported in the literature. Similarly, this is the first case of phrenic paralysis due to involvement of the nuclear region of the phrenic nerve by the zoster virus. The mechanism was similar to that of paralysis of the phrenic nerve associated with anterior poliomyelitis. All possible other etiologic mechanisms of diaphragmatic paralysis were excluded. This, plus the temporal sequence after the attack of zoster and the fact that the zoster did involve at least the third and fourth cervical segments, as evidenced by the cutaneous lesions, makes the relationship between the infection with zoster virus and the paralysis of the phrenic nerve conclusive. Whether the infection was introduced during the venipuncture when the patient served as a blood donor could not be judged.

CONCLUSIONS

Involvement of the motor nervous system by zoster, either through attacking the anterior horn or the cranial nuclei or through actual disease of the nerves is not at all unusual, as manifested by pathologic studies. Despite the frequent involvement of the anterior gray matter, motor manifestations are not usually detected with the anticipated frequency. The reasons for this discrepancy are discussed in the section on correlation of the pathologic and clinical picture. It is important that every patient with zoster be scrutinized for motor manifestations; especially should the muscles innervated by the affected segments be routinely tested. This procedure would serve several purposes. First, the true incidence of motor manifestations would become known; second, criteria for diagnosing those unusual cases of muscular paresis, with or without neuralgias, which are due to *zoster sine herpete*[30] might possibly be established; third, errors in diagnosis would be avoided—for example, the case reported here could have been diagnosed properly at its onset had these considerations been thought of, and, fourth, a more accurate concept of the pathogenesis and nature of zoster would emerge from more careful clinical observations.

30. Aitkin and Brain.[10a] Spillane.[10b] Weber.[9]

SUMMARY

1. Motor manifestations are an integral part of the neurodermatologic disorder zoster and are a result of the basic pathologic process.

2. Motor symptoms, especially those of a mild and transitory nature, occur frequently and will be found more frequently if specifically looked for.

3. Permanent destruction of motor neurons in the anterior horns or of the nuclei of origin of the motor cranial nerves may result in permanent paralysis.

A case is presented in which permanent paralysis of the phrenic nerve resulted after an attack of zoster.

Q FEVER IN A VETERANS' HOSPITAL

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Q FEVER as a new disease entity was first recognized and reported by Derrick [1] in 1937. He stated that the first case of this disease probably occurred in Queensland, Australia, in 1933. Davis and Cox [2] recognized and described the first case in the United States, and they termed the disease "nine mile fever" because of its occurrence in Nine Mile Creek, Mont. Since that time, numerous outbreaks of the disease in various parts of the United States, Panama and Italy have been described.[3] The demonstration of specific antibodies in the blood of persons living in Idaho, Montana, Wyoming, Nebraska, Nevada, Arizona

From the Medical Service of the Birmingham Veterans Administration Hospital.

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1. Derrick, E. H.: "Q" Fever: A New Disease Entity; Clinical Features, Diagnosis and Laboratory Investigation, M. J. Australia **2**:281-299, 1937.

2. Davis, G. E., and Cox, H. R.: A Filter-Passing Infectious Agent Isolated from Ticks, Pub. Health Rep. **53**:2259-2267, 1938.

3. (*a*) Robbins, F. C., and Ragan, C. A.: Q Fever in Mediterranean Area: Report of Its Occurrence in Allied Troops, Am. J. Hyg. **44**:6, 1946. (*b*) A Laboratory Outbreak of Q Fever Caused by the Balkan Grippe Strain of Rickettsia Burneti, Commission on Acute Respiratory Diseases, Fort Bragg, North Carolina, ibid. **44**:123-157, 1946. (*c*) Feinstein, M.; Yesner, R., and Marks, J. L.: Epidemics of Q Fever Among Troops Returning from Italy in the Spring of 1945: Clinical Aspects of the Epidemic at Camp Patrick Henry, ibid. **44**:72-87, 1946. (*d*) Shepard, C. C.: An Outbreak of Q Fever in a Chicago Packing House, ibid. **46**:185-191, 1947. (*e*) Huebner, R. J.; Jellison, W. L.; Beck, M. D.; Parker, R. R., and Shepard, C. C.: Q Fever Studies in Southern California, Pub. Health Rep. **63**:214-222, 1948. (*f*) Irons, J. V., and Hooper, J. M.: Q Fever in the United States: Clinical Data on an Outbreak Among Stock Handlers and Slaughterhouse Workers, J. A. M. A. **133**:815-818 (March 22) 1947. (*g*) Huebner, R. J.: Report of an Outbreak of Q Fever at the National Institute of Health, Am. J. Pub. Health **37**:431-440, 1948. (*h*) Cheney, G., and Geib, W. A.: The Identification of Q Fever in Panama, Am. J. Hyg. **44**:158-172, 1946. (*i*) Hornibrook, J. W., and Nelson, K. R.: An Institutional Outbreak of Q Fever, Pub. Health Rep. **55**:1936-1945, 1940.

and Washington [4] and the natural occurrence of epidemics in Texas,[5] Illinois [3d] and California [3g] attest to the widespread distribution of this disease in the United States. Numerous laboratory outbreaks among technicians working with this rickettsial organism have also been reported.[6] From 1937 to 1944 more than 217 cases were reported in Australia.[7] More than 200 cases of Q fever with positive diagnosis have been observed in Los Angeles County during the past year. Prior to this recent epidemic in California most of the cases described have occurred in laboratory technicians, meat workers and dairy farmers.

The causative agent of Q fever was first isolated by Burnet in Australia [8] and was given the name Rickettsia burneti by Derrick. He identified the typical rickettsial bodies in sections and smears of infected mouse livers and spleens. Cox [9] isolated the organism first in America, and suggested the name "Rickettsia diaporica." However, Burnet and Freeman [10] showed that the rickettsia isolated by Cox was immunologically indistinguishable from the rickettsia of Australian Q fever. Recently the name Coxiella burnetii has been suggested and accepted for this causative organism. C. burnetii (diaporica) is a minute, gram-negative, pleomorphic organism that occurs both intracellulary and extracellularly in affected tissues. It stains well with Giemsa stain and passes through N and W Berkefeld filters but fails to pass through a single Seitz disk.[9]

The mode of transmission of this disease has not been definitely ascertained. That cattle serve as a reservoir of the organism has been definitely established. That the agent is highly infectious has been shown by the high incidence of infection among persons known to have been exposed. As previously noted the incidence is highest in those engaged as dairy farmers or meat handlers. Whether a parasite may serve as the vector in transmission is still being investigated. C. burnetii has

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4. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 7, Philadelphia, The Blakiston Company, 1944.

5. Topping, N. A.; Shepard, C. C., and Irons, J. V.: Q Fever in the United States: Epidemiologic Studies of an Outbreak Among Stock Handlers and Slaughterhouse Workers, J. A. M. A. **133**:813-815 (March 22) 1947.

6. Burnet, F. M.; Freeman, M.; Derrick, E. H., and Smith, D. J. W.: The Search for Immunological Relationship Between "Q" Fever and Other Rickettsioses, M. J. Australia **2**:51-54, 1939. Footnote 3 *a*, *b* and *i*.

7. Derrick, E. H.: The Epidemiology of Q Fever, J. Hyg. **43**:357-361, 1944.

8. Burnet, F. M., and Freeman, M.: Experimental Studies on the Virus of Q Fever, M. J. Australia **2**:299-305, 1937.

9. Cox, H. R.: Rickettsia Diaporica and American Q Fever, Am. J. Trop. Med. **20**:463-469, 1940.

10. Burnet, F. M., and Freeman, M.: A Comparative Study of Rickettsial Strains from an Infection of Ticks in Montana (U. S. A.) and from Q Fever, M. J. Australia **2**:887-891, 1939.

been isolated from ticks in several parts of the United States.[11] Huebner [3g] failed to transmit the disease to guinea pigs by the injection of ground insects and other arthropods found on or in the vicinity of infected cows. Derrick [1] stated that the blood and urine of diseased guinea pigs would transmit the infection; however, Huebner [3g] failed to transmit the disease to guinea pigs inoculated with blood, urine or feces of diseased cows. From 10 to 20 per cent of the dairy cows in the Los Angeles area possess significant serum antibodies for Q fever, but no perceptible illness is noted in these animals.[3g] In a laboratory outbreak of Q fever, 9 of 11 technicians in one room engaged in culturing the organism contracted the disease. The 2 who remained healthy were the only workers who wore masks while engaged in this work.[3b] This incident points to the possibility of air-borne transmission of the infective agent. Epidemiologic studies of an outbreak among stock handlers and slaughterhouse workers in Texas also cast suspicion on the air-borne mode of transmission. This mode of transmission with subsequent inhalation of the organism has been suggested by recent investigations in Los Angeles County.[3g] The inhalation of dust contaminated with droplets of infected cows' milk wasted during the process of milking may be involved in this mechanism. The disease is probably not transmitted by ingestion of milk, and pasteurization apparently renders milk non-infectious. No instance of transmission of the disease from person to person has been noted.

The pathologic changes caused by Q fever in man have not been adequately described. The mortality rate is very low, and in those patients who died of this disease the diagnosis was not suspected and the pathologic changes were not adequately observed. In a fatal human case reported by Lillie, Perrin and Armstrong,[12] the gross pathologic abnormalities were pulmonary edema and congestion, a firm granular consolidation of the upper lobe of the right lung posteriorly and a large soft spleen. Much fibrin and a moderate mononuclear cell reaction were observed microscopically in the alveoli and bronchioles; however, the rickettsia was not demonstrated histologically. These authors noted similar pathologic changes in the Rhesus monkey. Longcope [13] in 1940 published in detail the pathologic findings in 2 autopsy cases of bronchopneumonia of unknown cause. It is probable that these deaths were due

11. Parker, R. R., and Kohls, G. M.: American Q Fever: The Occurrence of Rickettsia Diaporica in Amblyomona Americanum in Eastern Texas, Pub. Health Rep. **58**:1510-1511, 1943. Davis and Cox.[2]

12. Lillie, R. D.; Perrin, T. L., and Armstrong, C.: Institutional Outbreak of Pneumonitis: Histopathology in Man and Rhesus Monkeys in the Pneumonitis Due to the Virus of "Q" Fever, Pub. Health Rep. **56**:149-155, 1941.

13. Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X): A Report of Thirty-Two Cases with Two Deaths, Bull. John Hopkins Hosp. **67**: 268-305, 1940.

to Q fever. However the diagnosis cannot be accepted with certainty, as it was not confirmed by any established laboratory procedure. Recently, in Los Angeles County, autopsy in a case of suspected Q fever revealed lobar pneumonia of a fibrinous type with focal hemorrhages into the alveolar spaces. The microscopic picture consisted in an infiltration of round cells, giant cells and mononuclears with an almost complete absence of polymorphonuclears.[14] Large friable spleens and subcutaneous indurated nonsuppurative inflammatory reactions were noted grossly in infected guinea pigs.[3e] Parker and Kohls [11] noted similar changes in guinea pigs and also observed that the lymph nodes were enlarged and injected. The gross pathologic observations at autopsy in a fatal case of Q fever have recently been described by Brown, Knight and Jellison.[15]

It is generally accepted that one attack of Q fever confers immunity of indefinite duration. In controlled studies, it was noted that one laboratory infection in guinea pigs confers a permanent immunity.[1] This immunologic response is utilized in establishing the diagnosis of Q fever in human beings. No cross immunity with other rickettsial infections has been noted.[9] Serum from patients or animals suffering from most of the known rickettsioses give a negative agglutination reaction with emulsions of C. burnetii. The persistence of immunity may be partially related to the observation in experimental animals that the infectious agent may be recovered from the spleen, liver, lungs, brain, testes and seminal vesicles at least one hundred days or more after inoculation.[16] Corroborating evidence of the immunity conferred by Q fever will be noted later, when diagnostic tests and possible prophylactic vaccination are considered.

CLINICAL FEATURES OF Q FEVER

We have observed 12 cases of Q fever with positive serologic diagnoses during the past year. It must be borne in mind that the clinical features of Q fever as presented here are those of cases in which the symptoms are severe enough to necessitate hospitalization. As it can be assumed that all persons who show a positive serologic reaction for Q fever have been exposed to infection by C. burnetii, it may be concluded, since these persons give no history of any symptoms that may have been a manifestation of disease, either that in the majority of cases of Q fever there are no symptoms or that symptoms similar to those of an acute infection of the upper respiratory tract are so mild as to pass unnoticed.

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14. Denlinger, R. B.: Unpublished data.

15. Brown, D. C.; Knight, L. A., and Jellison, W. L.: A Fatal Case of Q Fever in Southern California, California Med. **69**:200-203, 1948.

16. Parker, R. R., and Steinhaus, E. A.: American and Australian Q Fever: Persistence of the Infectious Agents in Guinea Pig Tissues After Defervescence, Pub. Health Rep. **58**:523-527, 1943. Davis and Cox.[2]

All our patients were Caucasians, and all were men. Their ages ranged from 23 to 47 years. Most of the patients with acute infectious diseases seen at this hospital are in this age group. The disease has been diagnosed in patients from 3 [14] to 68 [3g] years of age. Proximity to dairies by reason of occupation or residence was regarded as a common factor in the histories of 50 per cent of the patients seen in this country.[3e] Three of our patients worked in dairies; 6 lived in the neighborhood of milk farms. One patient was bitten by a cat four days prior to the onset of the illness; this patient slept with a pet dog.

INCUBATION PERIOD

It was impossible to determine the incubation period in any of our cases. Derrick [1] reported it to be fifteen days or less. In the outbreak of Q fever in a Chicago packing house, Shepard [3d] expressed the belief that the incubation period was from nineteen to twenty-five days while a period of eleven to sixteen days was reported by another group.[3b] In guinea pigs, the time between inoculation of the infective agent and the onset of illness varied between two and eighteen days.

ONSET OF ILLNESS

Our patients entered the hospital from two to seven days, with an average of four days, after the onset of symptoms. The onset of illness was considered to be acute in 7 cases and insidious in 5. In most other series the onset was considered to be acute; however, Feinstein, Yesner and Marks [3c] reported an insidious onset in 70 per cent of 143 cases. Chills and fever, malaise, pain in the chest, headache, dizziness, vague aches and pains and anorexia were regarded in that order of frequency as the symptoms at the onset of the illness. Hornibrook and Nelson [31] have reported two types of onset: one coryza-like, and the other associated with headache, chills and malaise. Diarrhea, photophobia, articular pain, nausea and vomiting were noticed by others as initial symptoms.

COURSE OF ILLNESS

Most of the patients entered the hospital at the beginning of the height of the disease and at entry had already had most of the symptoms that were observed during hospitalization. Nine of 12 patients had been seen by physicians before entrance, and 3 had received penicillin and a sulfonamide before entry. In all cases the objective physical signs were slight in comparison to the symptoms and the height of the fever.

Fever.—All our patients had fever before entrance into the hospital. The temperatures on admission ranged between 98.8 and 105 F. with an average of 102.3 F. Five had initial temperatures above 104 and 9 above

102 F. The temperature tended to remain high; multiple spikes occurred, probably owing to the effect of salicylate and antipyretic therapy. The highest temperature recorded was 106.2 F.; however, the temperature was above 105 F. in 5 patients and above 104 F. in 11 at some time during hospitalization. In these 11 the temperature was above 104 F. for an average of 4.5 days after admission, with a range of from two to seven days. The duration of the fever was from four to twelve days, with an average of 7.8 days. Subsidence of fever was by rapid lysis; only 2 patients had a definite crisis. These observations are consistent with those of most other reports,[17] although Derrick [1] observed several cases in which the fever was low grade and protracted. In the 143 cases reported by Feinstein, Yesner and Marks,[3c] 21 patients had no fever while in the hospital and the temperature was elevated above 102 F. in less than half of the patients. The duration of fever was observed by Irons and Hooper [3f] to be from one to two weeks.

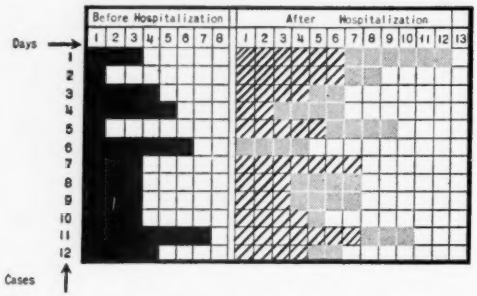

Chart 1.—Duration of fever. Cross-hatched blocks indicate temperature above 104 F.; dotted blocks, temperature above 98.6 F.

Pulse Rate.—It is generally stated that patients with Q fever show a relative bradycardia early in the disease.[18] On entrance the pulse rate ranged between 70 and 124, with an average of 96.5, beats per minute in our cases. One patient with a temperature of 104 F. had a pulse rate of 70, while another with a temperature of 104.8 F. had a pulse rate of 85 on admission. However, other patients had pulse rates that were consistent with the elevation in temperature. During hospitalization the pulse rate ranged between 70 and 100 and showed little relationship to the degree of fever. It can therefore be stated that a relative bradycardia is consistent with the diagnosis of Q fever; however it is not essential in considering this disease.

17. Foonote 3 *a*, *b*, *d*, *f* and *i*.

18. Footnote 1 and footnote 3 *a*, *b*, *c* and *i*.

Chills and Perspiration.—Chills and profuse sweating were noted in 10 and 11 of our patients respectively. Sweating was usually of such a degree as to necessitate a change of bed linens. Chills were of moderate severity in most cases; however, occasionally they were frank rigor. These symptoms persisted during the duration of temperature above 102 F. Chills and profuse perspiration have been noted as common symptoms in all the reported series of cases.

Malaise and Weakness.—Malaise and weakness were noted in all our patients and were regarded as the initial symptoms in 5. These were the most persistent complaints of our patients and were still present in 5 at the time of discharge. One patient suffered from excessive fatigue for as long as three months after the onset of his illness. Generalized muscular

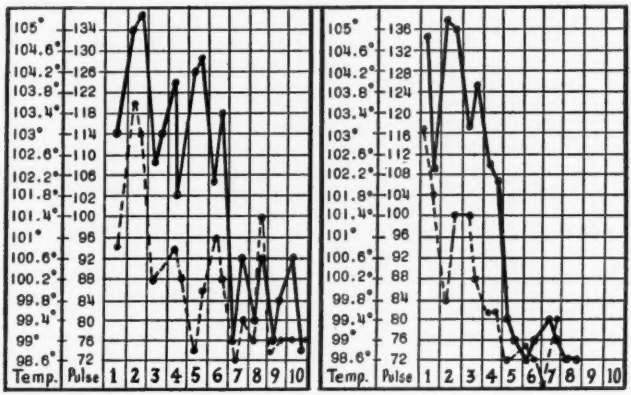

Chart 2.—Graphic representation of temperature (solid line) and pulse rate (dotted line).

aches and pains were noted in six cases. These observations are consistent with the experience of others.

Respiratory System.—In 9 of our 12 patients, pneumonitis was demonstrated on roentgenologic examination. Of the 3 without pneumonitis, 1 complained of severe pain in the chest, and this symptom persisted for three days. The other 2 patients had no symptoms referable to the respiratory tract. Of the 9 patients with pulmonary involvement, 5 complained of thoracic pain at some time during the illness. This pain was usually of moderate severity and of short duration. The respiratory rate was essentially normal with slight transient elevation. In 1 patient with pneumonitis, there was a transient increase in the respiratory rate to 45 per minute. Eight patients had a cough, usually dry. Slight expectoration was present in 4, and hemoptysis was present in 3. Despite

the presence of pneumonitis, the respiratory symptoms and signs were not conspicuous. In one reported series of cases,[3i] more than half of 15 patients with pneumonitis complained of vague thoracic pain in the substernal region that was not related to respiration. Shepard [3d] and Robbins and Ragan [3a] noted pain in the chest in half of their patients and stated that this was rarely a true pleuritic pain but was rather of a neuralgic character. In another series,[3c] pleuritic pain was present in 35 per cent of 143 cases. In other reports expectoration was minimal and blood tinged-sputum infrequent. Derrick [1] did not include the presence of pneumonitis as part of the syndrome, but in all subsequent epidemics of Q fever, pulmonary involvement was mentioned in the majority of cases.

Gastrointestinal System.—All our patients complained of anorexia, and 8 had nausea and vomiting. These symptoms usually persisted for one or two days; however, in 1 case vomiting lasted for eight days even though only small amounts of fluid were given orally. This patient also experienced postcibal vomiting twenty-five days after admission, and this persisted until the time of discharge, eight days later. Nausea and vomiting were recorded frequently by other investigators.[19] Abdominal pain was prominent in 2 cases. This was vague and referred to the epigastrium and right upper quadrant. Diarrhea of one day's duration was present in 1 case; constipation was not recorded in any case. Derrick [1] reported constipation as being a prominent feature of the disease, and it was also present in 33.6 per cent of 143 patients in a series reported by another author. Robbins and Ragan [3a] observed a few patients with gastrointestinal complaints, including diarrhea.

Headache.—Headache was reported as the outstanding symptom of Q fever by many authors.[20] It was described as severe and persistent. Robbins and Ragan [3a] described the headache as mainly frontal with retro-orbital pain on movement of the eyeballs, while nuchal pain was most frequent in other instances.[5] Shepard [3d] stated that none of 33 patients mentioned headache until directly questioned and even then most said that they had not had this symptom. As stated previously, 2 patients experienced headache as the initial symptom, and 11 patients suffered from it at some time during their illness. Headache was severe and persistent, lasting an average of six days, with the longest duration fourteen days. The headache was frontal in those cases in which the location was recorded. Codeine was often necessary for relief.

Neurologic Findings.—Two of 11 patients complained of dizziness, while 1 had this as the initial feature of his disease. Stupor and confusion were noted in 2 cases; restlessness and insomnia were commonly

19. Footnote 1 and footnote 3 *a*, *c*, *d* and *i*.

20. Footnote 1 and footnote 3 *a*, *b* and *i*.

observed during the acute stage of the disease. Derrick [1] observed drowsiness and stupor in his most severely ill patients and classified these patients as showing the typhoidal type of the disease. These observations were consistent with those in other reported cases.

Miscellaneous Symptoms.—Epistaxis was noted in 1 case, but it was not severe and was of short duration. Frequency and burning on urination were observed in 1 case. We have the impression that most of our patients lost some weight during hospitalization, but the weight loss was recorded in only 1 case; in this case it was 22 pounds (10 Kg.). Photophobia was present in 2 cases. All these symptoms, except frequency and burning on urination, were mentioned infrequently in other reports. However, Derrick [1] observed photophobia as a common symptom in his cases.

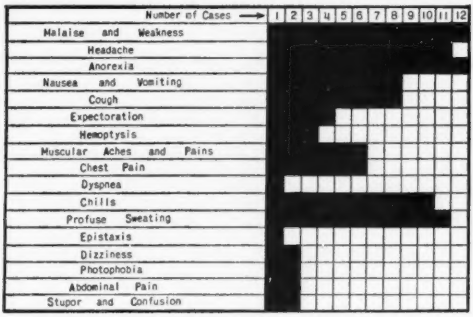

Chart 3.—Incidence of symptoms.

Physical Findings.—The significant observations on physical examination in Q fever are usually scant. Six of our 12 patients appeared in acute distress on admission. Four appeared moderately ill, and 2 seemed to be well. Four of the patients were described as having flushed facies. Three had a light yellow-coated tongue. A slightly injected pharynx was observed in 8 patients, a condition which was described in other series.[3a, e] The conjunctivas were congested in 2 patients. Stiffness of the neck was seen in 3 of 15 cases by Hornibrook and Nelson [31] and was also observed by Robbins and Ragan.[3a] Moderate nuchal spasm was observed in 2 of our patients. Lymph nodes were palpable in 5 of our patients; however, this condition was rarely recorded in other reports. Splenomegaly and hepatomegaly were not observed in any of our patients and have been found to be rare in Q fever. A cutaneous rash was present in 4 of our patients at some time during the illness. It was

present in only 1 patient on admission and was described as a fine confluent red rash involving the face, chest, shoulders and back. It faded rapidly in two days. The remaining 3 patients had been given penicillin, and in 2 of them the skin manifestations were probably a sensitivity reaction to the antibiotic. A typical rash is unusual in Q fever, but Derrick [1] described its presence in 1 of 7 patients. Physical findings on examination of the chest were usually slight. They were completely absent in 2 patients with pneumonitis. In 7 patients with pneumonitis there were fine crepitant rales; in 5, bronchial breath sounds; in 2, increased vocal fremitus, and in 1, impaired resonance and respiratory lag. These conditions persisted for four to six days after admission; however, in 1 patient thoracic abnormalities persisted until the eighteenth day. Signs when present were always over the area of pulmonary involvement. Hornibrook and Nelson [31] reported absence of thoracic abnormalities in 15 cases of pneumonitis. Fine rales were observed in most reported cases.[21] In another series a friction rub was found in 5 of 15 patients with pneumonitis. In most patients these findings were transient. Derrick [1] did not consider pneumonitis as part of the disease in his original report. An apical systolic murmur was recorded in 2 cases. Abdominal tenderness with moderate distention and costovertebral tenderness were found in 1 each of our patients. Derrick [1] reported the presence of jaundice in 1 patient.

Convalescence.—Convalescence was usually rapid after patients were admitted to the hospital. They became relatively asymptomatic from six to fifteen days after admission, with an average of 10.9 days. However, residual weakness and fatigue persisted in 5 patients, in 1 lasting for three months after discharge from the hospital. One patient complained of postcibal nausea and occasional vomiting of about one month's duration after discharge. The average duration of hospitalization was 19.2 days One patient recently returned to the hospital, nine months after onset of illness, complaining of fever, malaise and muscular pains; the complement fixation test for Q fever elicited a positive reaction in a titer of 1:64, and his temperature on admission was 100 F.; no other cause for his illness could be ascertained. Robbins and Ragan [3a] reported a protracted course in severe cases and an average hospitalization of twenty-two days. Feinstein, Yesner and Marks [3c] observed an average duration of illness of four days. Derrick [1] stated that convalescence was variable and recovery was not complete in some cases for as long as five months. Arthritis, orchitis and epididymitis were observed as late complications in one series,[5] and ascites, jaundice, pedal edema and heart failure were reported in cases from Australia.

21. Footnote 3 *a*, *b* and *c*.

LABORATORY OBSERVATIONS

Blood.—Several blood counts were done in all our cases. The red blood cell count was never above 5,000,000 on entry, and in only 2 did it reach that figure at any time during hospitalization. Five patients had a count below 4,000,000 on one occasion each, usually about four days after admission. One patient had 2,040,000 red blood cells per cubic millimeter on admission, but the count rapidly became normal without specific therapy. The white blood cell count varied between 3,600 and 14,200. Seven patients had a white cell count below 6,000 on at least one occasion, and only 5 had an elevation of the white blood cells above 10,000 during hospitalization. A differential count showed the neutrophils above 70 per cent in all cases on entry, while the lymphocytes were below 25 per cent. There was an increase in the percentage of lymphocytes in all patients, and on recovery the number of these cells usually

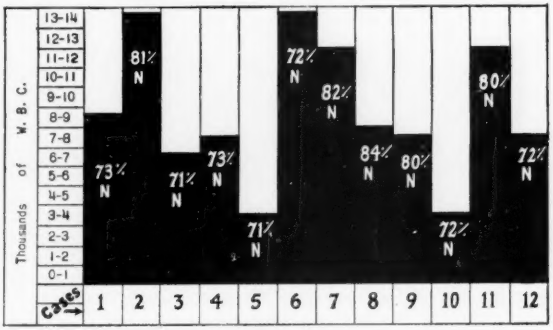

Chart 4.—Initial leukocyte counts.

approximated that of the neutrophils. The sedimentation rate was elevated in all patients and was above 25 mm. per hour in 9. These observations are consistent with those reported by other authors.[22]

Urine.—Albuminuria, 1 or 2 plus, occurred in 8 patients and disappeared when the temperature subsided. A few cellular elements and casts were found in most instances. Occasional albuminuria has been reported in all other series.

Roentgenograms of the Chest.—The pneumonitis of Q fever presents a variable roentgenologic picture. A patchy infiltration was present in 6 of our patients, a diffuse homogeneous density in 2 and a fine confluent infiltration in 1. Any one or several lobes may be involved in the process. In our patients the middle and lower lobes of the right lung

22. Footnote 1; footnote 3 *a*, *b*, and *c*; footnote 5.

were involved in 3; the lower and middle lobes of the right lung, in 2; the upper lobe of the right and of the left lung in 1, and the upper lobe of the right lung, the upper lobe of the left lung and the lower lobe of the left lung separately, in 1 case each. On repeat roentgenograms made four to eight days after admission, an increase in the extent of involvement was noted in 7 cases. Regression of the pulmonic infiltration occurred,

TABLE 1.—*Roentgen Changes Observed in Patients with Pneumonitis*

	Day															
Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1.....	+	..	..	..	I	..	..	..	..	..	..	..	..	..	..	C
2.....	+	..	..	I	..	..	..	I	..	..	..	..	C	..	..	..
3.....	+	..	..	..	..	..	..	..	..	..	..	..	C	..	..	..
4.....	+	..	..	..	..	S	..	..	..	..	..	C	..	..	..	..
5.....	+	..	I	..	..	I	..	..	..	..	..	..	C	..	..	..
6.....	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
7.....	+	..	..	..	I	..	..	..	C	..	..	..	..	..	..	..
8.....	+	..	..	..	I	..	..	..	..	..	..	..	..	..	..	C
9.....	+	..	I	..	..	..	I	..	..	C	..	..	..	C	..	..

Explanation of symbols: +, infiltration present; I, increased; S, no change; C, clearing. In case 6 roentgenograms were not repeated.

TABLE 2.—*Results of Laboratory Studies*

	Day											
Procedure	1	2	3	4	5	6	7	8	9	10	11	12
Roentgenograms	+	+	+	+	+	+	+	—	—	—	+	+
Blood cultures.....	—	—	..	..	—	—	—	—	—	—	..	..
Serologic tests.....	—	—	—	—	—	—	—	—	—	—	—	—
Spinal tap.....	—	..	..	..	..	..	..	—	..	..	..	..
Sputum examination.....	—	+*	..	..	+†	..	..	—	—	—	—	—
Electrocardiogram	—	—	..	..	—	..	—	..	..	+‡	—	..
Urinalysis (albumin).....	+	+	+	—	+	+	—	+	+	+	+	+
Liver function tests.....	+	..	..	—	..	..	..	..	..	—	..	..
Malarial smears.....	—	—	..	..	—	..	—	—	—	—	..	..
Cold agglutination.....	—	—	—	..	—	—	—	—	..	..	..	..
Heterophile agglutination.....	—	—	—	..	—	—	—	—	—	—	—	..
Agglutination for Brucella A....	—	—	..	..	—	—	—	—	—	—	—	..
Agglutination for typhoid A....	—	..	..	..	—	—	—	—	..	—	..	..
Agglutination for paratyphoid A	—	..	..	..	—	—	—	—	..	—	..	..
Agglutination for tularemia....	—	..	..	..	..	..	—	..	..	..	—	..
Weil-Felix test.....	—	—	..	..	—	—	—	—	—	—	—	..

* Aspergillus cultured.
† K. pneumoniae type B cultured.
‡ Left axis deviation shown.

usually by the twelfth to the sixteenth day. However, in no case did the roentgenogram of the chest taken at the time of discharge show completely normal conditions. One patient was followed with chest roentgenograms at regular intervals for three months after discharge, and residual increased vascular markings were noted during that entire period. The roentgen findings were interpreted as being consistent with an

atypical pneumonia in 7 cases and as a pneumonic consolidation in 2 cases. Robbins and Ragan [3a] reported pulmonary involvement in 190 of 266 cases. They stated that the lower lobes were more frequently involved and that a minimal effusion was noted in 4 of 51 cases. Our observations and the persistence of the pneumonic process are consistent with other reports, but Feinstein, Yesner and Marks [3c] stated that in 102 of 147 cases of pneumonic involvement, the roentgenogram of the chest revealed normal conditions after an average of 10.8 days.

Other Laboratory Studies.—Spinal puncture with examination of fluid was done in the 2 cases with nuchal rigidity. Dynamics and chemical constituents were normal and culture negative. In the infrequent reports of this examination in other series the results of spinal fluid examination have been negative.[31] Studies of sputum in 8 cases showed the usual flora in 6, minimal growth of Aspergillus in 1 and Klebsiella pneumoniae type B in 1. Results of hepatic function tests done in 3 cases were normal in 2; 1 patient had an icteric index of 10.8 and increased urobilinogen in the urine on three examinations. Electrocardiograms were made in 6 cases; 5 showed no abnormalities, and 1 showed left axis deviation. Routine and cold agglutination tests, Wassermann tests, heterophile agglutination tests, Weil-Felix tests, smears for malaria and blood cultures were done in the majority of our cases, and results were reported as negative.

DIAGNOSIS

The diagnosis of Q fever depends on the demonstration of a positive reaction following a negative one or a significant rise, fourfold or greater, in the complement fixation titer of the patient's serum. Blood for this determination should be drawn as soon as possible, preferably before the ninth day of illness and again fourteen to twenty-one days later. Agglutination tests for Q fever were first described by Burnet and Freeman [8] at the time of the discovery of this disease. The complement fixation reaction becomes positive usually after the ninth day of illness. However, in 1941 Bengtson [23] reported that in the complement fixation test the antibodies were present in human serum thirteen days after the onset of the fever. The titer of the serum increased in twenty-two to twenty-three days and she found a titer of 1 : 32 in 2 of 13 cases on the three hundred and eighty-fifth and three hundred and fifth day respectively after onset. A rise in titer in the complement fixation test, however mild the disease, is regarded as definite evidence of Q fever. The diagnoses in our cases, as in all other reports, were made by this serologic test. However, in some epidemics [24] demonstration of the rickett-

23. Bengtson, J. A.: Complement Fixation in Q Fever, Proc. Soc. Exper. Biol. & Med. **46**:665-668, 1941.

24. Smadel, J. J.; Snyder, M. J., and Robbins, F. C.: Vaccination Against Q Fever, Am. J. Hyg. **47**:71-81, 1948. Burnet and Freeman.[8]

sial organism by inoculation of guinea pigs confirmed the diagnoses. The Weil-Felix reaction was negative in our cases, as in other reported series.[25]

The admitting diagnoses were: atypical pneumonia in 6 cases; atypical pneumonia, probably Q fever, in 1 case; fever, origin undetermined, in 2 cases; influenza in 2 cases, and lobar pneumonia in 1 case. Q fever was listed as a disease to be ruled out in 3 other patients. Infectious mononucleosis, malaria, pyelitis, infectious hepatitis, brucellosis, poliomyelitis, meningitis and rheumatic fever were listed as possibilities in various cases. These diseases were also considered initially in other reports.[3a, d] Grip, infection of the upper respiratory tract, bronchitis, gastroenteritis and tuberculosis were initial diagnoses in other series.[3d]

One patient showed a definite psychotic reaction for three days during the height of the illness. This case will be reported elsewhere.

INCIDENCE

Since September 1947 all patients admitted to the Medical Service of Birmingham Veterans Administration Hospital with an influenzal syndrome, atypical pneumonia or fever of undetermined origin were tested routinely for Q fever complement fixation immediately after admission and fourteen days or longer after the first test. The tests were performed at the Hondo Q Fever Laboratory of the United States Public Health Service, at Hondo, Calif., and since early 1948 in duplicate by our own laboratory and the laboratory at Hondo. We tested 93 patients with these diagnoses between Sept. 4, 1947 and July 31, 1948, when the compilation of this report was terminated. Among these 93 there were 20 with positive agglutination reactions for Q fever (21.5 per cent); hence it is obvious that the incidence of Q fever among patients seriously enough ill to be hospitalized with illness simulating influenzal syndrome, atypical pneumonia or fever of undetermined origin during this period of approximately eleven months was astoundingly high. From Aug. 1, 1948 to June 15, 1949, a similar period of approximately eleven months, we performed agglutination tests for Q fever on the serums of 201 patients with similar diagnoses and have obtained positive results in only 6 cases (2.98 per cent). Even admitted that the per cent difference in incidence of this disease during these two like periods was influenced possibly by the greater number of patients tested during the latter eleven month period, we feel that the difference in the numbers of patients with diagnoses of Q fever during these two periods is significant. Other

25. Irons, J. V.; Murphy, J. N., Jr., and Wolfe, D. M.: Q Fever in the United States: Serological Observations in an Outbreak Among Stock Handlers and Slaughterhouse Workers, J. A. M. A. **133**:819-820 (March 22) 1947.

reports of this disease in the literature refer to its as occurring in epidemics, but the groups of diseased persons described were compact and had similar exposure to the infective agent. Our patients came from widely separated areas in Los Angeles County. These facts tend to support a conclusion that Q fever may occur in epidemic form during certain periods and surely the incidence is so high during such periods that it commands attention among communicable diseases of epidemiologic interest.

MORTALITY

The mortality rate of Q fever is less than 1 per cent. We had no deaths from this disease at this hospital. Hornibrook and Nelson[31] reported 1 death among 15 patients. Two brothers died of Q fever during the Texas epidemic in 1946. There have probably been two deaths from Q fever in Los Angeles County. The gross observations at autopsy in 1 of these cases have been published.[15]

With the increase in the incidence of Q fever, methods of prophylaxis in persons with possible exposure by reason of occupation have been studied. In one report of a laboratory outbreak [3g] it was found that Rocky Mountain fever vaccine may give some protection against Q fever. Guinea pigs showed a definite resistance to the infection after vaccination; the duration of fever was shorter, and the mortality rate was decreased from 40 to 80 per cent to 2 per cent. In 28 vaccinated human patients complement-fixing antibodies were present in a significant titer.

TREATMENT

The management of Q fever at this hospital was similar to that reported in other places. Supportive therapy, which included forcing of fluids and use of analgesics, was administered in all cases. Intravenous administration of fluids was considered to be necessary in 6 cases, being given for an average of five days, with a duration of sixteen days in 1 case. Antispasmodics for the control of abdominal cramps were administered to 3 patients. Four of our patients received both sulfonamides and penicillin; 3 received sulfonamides alone; 3 received penicillin alone, and 2 received no chemotherapy or antibiotic therapy. When penicillin and sulfonamide drugs were given, they were administered for an average of 6.6 and 4.3 days respectively. No significant beneficial results were observed with these drugs. Our observations are consistent with results as reported by other workers.[26] Paraaminobenzoic acid, because of its beneficial effect in other rickettsial diseases, has been tried and has proved of little or no value. Experimentally, streptomycin has been observed to exercise a rickettsiostatic action on the growth of R. burneti in the yolk sacs of fertile eggs and to lower the

26. Footnote 3 *a*, *c* and *i*.

mortality rate in guinea pigs inoculated with highly virulent suspensions of R. burneti.[27] In a reported case of Q fever treated with streptomycin, clinical improvement was attributed as possibly due to the use of this drug.[28] A new antibiotic, aureomycin hydrochloride, has been shown to display exceptional curative powers in experimental Q fever in animals. It has been used in several cases of human Q fever and has been noted to exert a beneficial effect in some cases. However, it is not possible at present to evaluate conclusively the role of this drug in the therapy of Q fever. Aureomycin to be effective has to be employed early in the disease, prior to the time that the diagnosis can be established by serologic study. Hence, it has to be used empirically. However, even in those cases in which the drug is effective in controlling or aborting the disease, it does not interfere with antibody formation: therefore a positive serologic diagnosis may be made even if the patient has become asymptomatic.

In conclusion, it may be stated that Q fever is a protean disease, acute in character but with a variable course with widespread distribution throughout the U. S. and probably the world. It is probably caused by a rickettsial organism. Dairy farm and other animals probably served as a reservoir for the infection and transmission is probably an air-borne mechanism. It presents no definite distinguishable clinical features, and diagnosis depends on a high index of suspicion in any epidemic of acute illness and on a positive serologic reaction. The utilization of prophylaxis and specific therapy will probably be of benefit: however, these measures are still in the investigative stage.

SUMMARY

A brief review of the literature concerning Q fever is presented.

Twelve cases of Q fever with positive serologic study are summarized.

Clinical features of Q fever as observed in these cases are presented and compared to the reports from the literature of other cases of Q fever.

Therapy for this disease is discussed briefly.

The incidence of Q fever was 21.5 per cent in a group of hospitalized veterans admitted with the diagnosis of influenzal syndrome, atypical pneumonia or fever of undetermined origin during an eleven month period (1947-1948). In a similar eleven month period (1948-1949) the incidence was 2.98 per cent in patients admitted with similar diagnoses.

27. Huebner, R. J.; Hottle, G. A., and Robinson, E. B.: Action of Streptomycin in Experimental Infection with Q Fever, Pub. Health Rep. **63**:357-362, 1948.

28. Rosove, L.; West, H. E., and Bower, A. G.: Q Fever: Case Treated with Streptomycin. Am. Int. Med. **28**:1187-1193, 1948.

PATHOLOGY OF SUBCHRONIC ATROPHY OF THE LIVER

Comparison with Laennec's Cirrhosis

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DETAILS have already been published of a considerable number of fatal cases of chronic hepatitis [1] in Denmark during the years 1944 to 1947. The pathoanatomic picture corresponded to what was described in earlier literature as subchronic atrophy of the liver,[2] synonyms for which were subacute diffuse necrosis of the liver, subacute yellow atrophy of the liver, toxic cirrhosis and necrotic hepatitis.

The aim of this work is to give a detailed description of the pathologic changes in the liver in this rare disease on the basis of data obtained from considerable postmortem material.

We found it of interest to make a comparison with the cases of Laennec's cirrhosis in which autopsies were made during the same period, since subchronic atrophy of the liver offers clinically a number of points of similarity with Laennec's cirrhosis.

As a few biopsies of the liver were made, we endeavored to solve the problem of whether it is possible with the aid of biopsy at an early stage of the disease to distinguish subacute atrophy of the liver from acute hepatitis and from cirrhosis of the liver.

This study was supported by a grant from the King Christian X Fund.

From the Pathological Institute (Dr. S. Petri, Director and Chief Anatomist) and the Third Medical Department (Dr. Poul Iversen, Physician in charge), Kommunehospitalet.

1. (*a*) Bjørneboe, M., and Brøchner-Mortensen, K.: Prognosis in Acute Hepatitis, Ugesk. f. læger. **107**:715-718, 1945. (*b*) Jersild, M.: Increasing Frequency of Chronic Hepatitis, ibid. **107**:819-822, 1945; Infectious Hepatitis with Subacute Atrophy of the Liver, New England J. Med. **237**:8-13, 1947. (*c*) Alsted, G.: Studies on Malignant Hepatitis, Am. J. M. Sc. **213**:257-267, 1947. (*d*) Bjørneboe, M.; Jersild, M.; Lundbæk, K.; Hess-Thaysen, E., and Ryssing, E.: Incidence of Chronic Hepatitis in Women in Copenhagen, 1944-45, Lancet **1**:867-868, 1948.

2. Bergstrand, H.: Ueber die akute und chronische gelbe Leberatrophie mit besonderer Berücksichtigung ihres epidemischen Auftretens in Schweden im Jahre 1927, Leipzig, Georg Thieme, 1930.

Finally, on the basis of both groups of material, we tried to discover whether there is a connection between the size of the liver at autopsy and the occurrence of various symptoms, especially that of hepatic insufficiency.

Only scanty reports concerning the pathology of subchronic atrophy of the liver have been published. In Bright's work,[3] a typical case of the disease was described, but Marchand [4] was the first to recognize its relation to acute atrophy of the liver. Wilson and Goodpasture [5] described a single case and referred to older publications dealing with the subject.[6] Bergstrand [2] discussed, in his work on acute and chronic atrophy of the liver, 150 cases of these diseases. Eleven of them in which there were symptoms of the disease over a period of three months were presumably of the same nature as those described in this report. In the years following, a few similar cases were described. Lucké [7] reported in 1944 that among 125 fatal cases of hepatitis there were 7 of more than three months' duration from the first symptom until death.

In a condition of subchronic atrophy, the liver is as a rule greatly and uniformly reduced in size (fig. 1). The surface is smooth or wrinkled, and in cases of longer standing it is nodular. It is yellow and red. In the yellow parts the surface is domed, and in the red parts it is depressed. On the surface of the section, yellow "islands" are to be seen, separated by the red, depressed parts. Under the microscope, it is found that the liver parenchyma has completely disappeared in the red parts, where there are only vessels and connective tissue infiltrated with inflammatory cells with some "proliferation of the bile ducts." The yellow "islands" consist of cells of the liver parenchyma, to some extent with degenerative and necrotic changes. The trabecular structure is indistinct.

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3. Bright, R.: Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy, London, Longman [and others], 1828, p. 105, plate 6.

4. Marchand, F.: Ueber Ausgang der acuten Leberatrophie in multiple knotige Hyperplasie, Beitr. z. path. Anat. u. z. allg. Path. **17**:206-219, 1895.

5. Wilson, J. D., and Goodpasture, E. W.: Yellow Atrophy of the Liver: Acute, Subacute and Healed, Arch. Int. Med. **40**:377-385 (Sept. 27) 1927.

6. MacDonald, S., and Milne, S. L.: Subacute Liver Atrophy, J. Path. & Bact. **13**:161-173, 1909. Mallory, F. B.: Cirrhosis of the Liver: Five Different Types of Lesions from Which It May Arise, Bull. Johns Hopkins Hosp. **22**:69-75, 1911. Miller, J., and Rutherford, A.: Liver Atrophy, Quart. J. Med. **17**:81-100, 1923. Pratt, J. H., and Stengel, A.: Toxic Cirrhosis Resulting from Acute Liver Atrophy, Tr. A. Am. Physicians **41**:100-110, 1926. Strauss, H.: Ueber subacute Leberatrophie mit Aszites und dessen Beziehungen zur Leberzirrhose, Deutsche med. Wchnschr. **46**:487-488, 1920.

7. Lucké, B.: The Pathology of Fatal Epidemic Hepatitis, Am. J. Path **20**:471-527, 1944.

MATERIAL

Subchronic Atrophy of the Liver.—The material consisted of 108 cases in which autopsies were performed at the pathologic institute of Kommunehospitalet during the period from Jan. 1, 1944 to Jan. 1, 1948. Only 6 subjects were men, whereas 102 were women. This considerable preponderance of women, which was shown by Ryssing [8] to exist in a previous study, could not be explained. The age range of the dead subjects is shown in figure 2. It can be seen that the curve in the case of

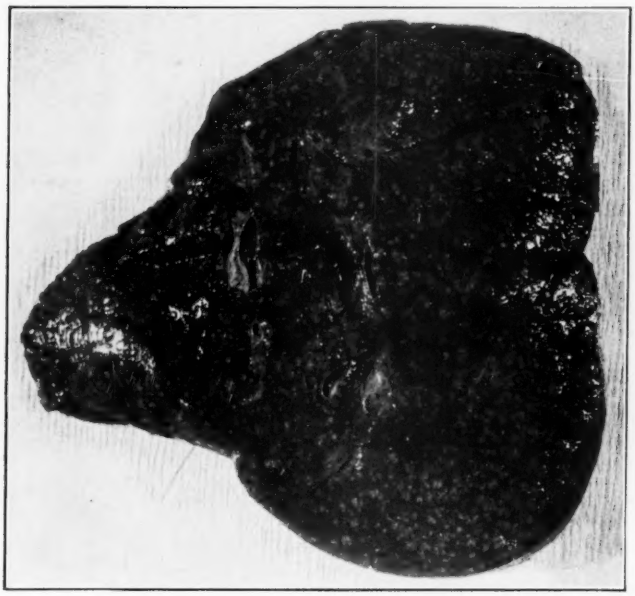

Fig. 1.—Cut surface of the liver of a woman of 71 with subchronic atrophy of the liver of five weeks' duration.

women rises steeply after the forty-fifth year, a circumstance which could not be explained.

With regard to the distribution of the material within the period from 1944 to 1948, it must be noted that autopsies were performed in 78 of the 108 cases between June 1945 and October 1946.

There are included in this group all cases in which the macroscopic picture corresponded to that of subchronic atrophy of the liver. In very

8. Ryssing, E.: Hepatitis in Copenhagen, Ugesk. f. læger. **110**:1099-1102, 1948.

few cases the diagnosis was in some doubt, as forms were noted which were in a state of transition toward Laennec's cirrhosis. In 1 instance chronic atrophy was even seen in one lobe of the liver and Laennec's cirrhosis in the other. By far the greater part of the material showed, however, a typical and uniform appearance.

Laennec's Cirrhosis.—This material consisted of all cases of Laennec's cirrhosis (portal cirrhosis) in which autopsies were made at Kommunehospitalet in the period from January 1944 to January 1948, or

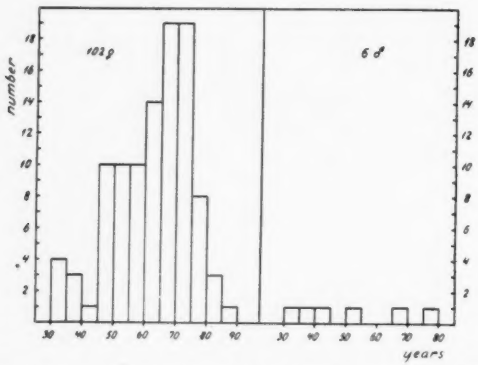

Fig. 2.—Age and sex distribution in subchronic atrophy of the liver.

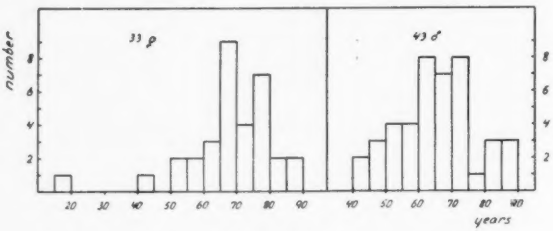

Fig. 3.—Age and sex distribution in Laennec's cirrhosis.

76 cases in all (cases of biliary cirrhosis or chronic stasis of the liver were excluded). Thirty-three subjects were women and 45 men, a distribution between the sexes essentially different from that in subchronic atrophy of the liver. The age range is shown in figure 3, which indicates that the maximum incidence fell within the age group of 60 to 80. No definite difference was seen between the distributions for men and women, nor did there appear to be any definite distinction in the age ranges in subchronic atrophy of the liver and in Laennec's cirrhosis.

On examination of the postmortem records from 1928 to 1947 inclusive (fig. 4), it was clearly seen that the number of cases of Laennec's cirrhosis had been relatively constant over those years (about 20 per year in 900 to 1,000 autopsies), whereas the number of cases of subchronic atrophy of the liver showed an enormous increase beginning in 1944; formerly, this type had appeared only sporadically. With regard to the distribution between the sexes, it can be seen that, whereas Laennec's cirrhosis had formerly occurred mainly in men (fig. 4), in the years 1944, 1945 and 1946 a relatively larger number of cases were recorded among women. We shall deal with this situation in more detail later in this report.

PATHOLOGIC ANATOMY

Macroscopic Anatomy.—Weight of the Liver: In 28 autopsies in cases of subchronic atrophy of the liver chosen at random (25.9 per cent

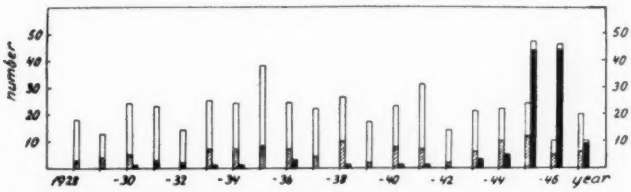

Fig. 4.—Occurrence of subchronic atrophy of the liver (columns on the right) and Laennec's cirrhosis (columns on the left) in postmortem material of Kommunehospitalet in the years 1928 to 1947. Shaded areas indicate female patients.

of the total cases of this condition), the weight of the liver was measured. In 7 instances it weighed less than 700 Gm., in 14 between 700 and 900 Gm. and in 7 over 900 Gm. In other words, there was a pronounced reduction of the liver parenchyma (the normal weight is 1,450 to 1,750 Gm.[9]).

Size of the Liver: In all autopsies, the measurements of the liver were given in the three planes. We multiplied these three figures together to form an estimate of the volume of the liver, knowing full well that that value could be at most only an approximate figure for the cubic content (hereinafter called the volume index). In figure 5 is shown the relation between the weight of the liver and the volume index in the 28 cases mentioned previously; a close correlation was

9. Tumen, H. J.: Anatomy and Physiology of the Liver, in Bockus, H. L., and others: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1946, vol. 3, p. 1.

noticed, and for that reason we later felt ourselves at liberty to use the volume index as a measurement for the size of the liver.

In figure 6 is the distribution according to the volume index for 104 cases of subchronic atrophy of the liver and 73 cases of Laennec's cirrhosis. Subchronic atrophy of the liver entails, as a whole, a con-

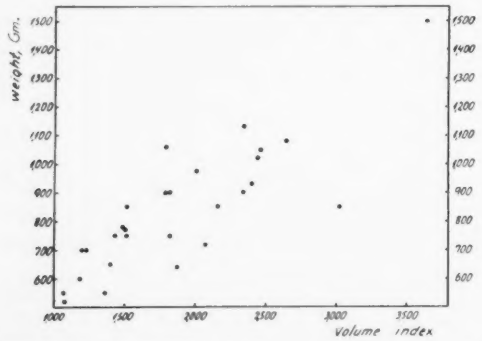

Fig. 5.—Relation between weight and volume index of the liver in 28 cases of subchronic atrophy of the liver.

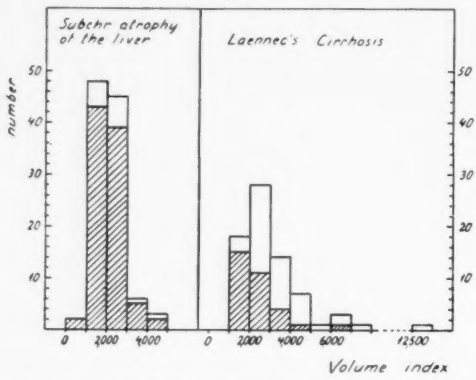

Fig. 6.—Volume index of the liver for 104 cases of subchronic atrophy of the liver and 73 cases of Laennec's cirrhosis. The shaded areas indicate death from hepatic coma.

siderably greater reduction of the liver than Laennec's cirrhosis: In 48 per cent of the cases of subchronic atrophy of the liver there was a volume index below 2,000, whereas in only 25 per cent of those of Laennec's cirrhosis was there a volume index below the figure.

Carcinoma of the Liver: Five instances of primary carcinoma of the liver (6.6 per cent of the total) and 4 of hepatomas were observed among the subjects with Laennec's cirrhosis, whereas neither disorder was observed among 108 with subchronic atrophy of the liver. Berk and Lieber [10] observed primary carcinoma in 4.5 per cent of the subjects with cirrhosis of the liver, whereas 67 per cent of those with primary carcinoma of the liver also had cirrhosis of the liver.

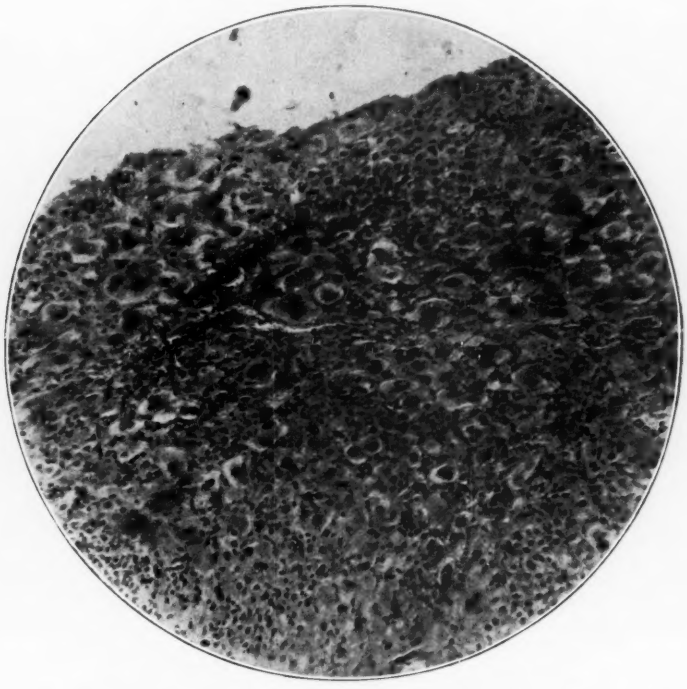

Fig. 7.—Biopsy specimen of the liver of a woman of 56 with subchronic atrophy of the liver, taken after two months' duration of symptoms. The duration of the disease to death was four and one-half months.

Cholelithiasis: Among the subjects with Laennec's cirrhosis there were 21 (28 per cent) with gallstones (2 of these had undergone cholecystectomy directly before death), whereas 20 (18.5 per cent) of the subjects with subchronic yellow atrophy of the liver had gallstones.

10. Berk, J. E., and Lieber, M. M.: Primary Carcinoma of the Liver in Hemochromatosis, Am. J. M. Sc. **202**:708-714, 1941.

In all instances in subchronic atrophy of the liver this disorder is a matter of small pigment stones, presumably formed during the course of the disease.[11] The cases in which the diagnosis was assumed beforehand to be biliary cirrhosis were not included in the material. The figures were scarcely higher than could be expected according to the age range and the sex distribution of the types of material.[12]

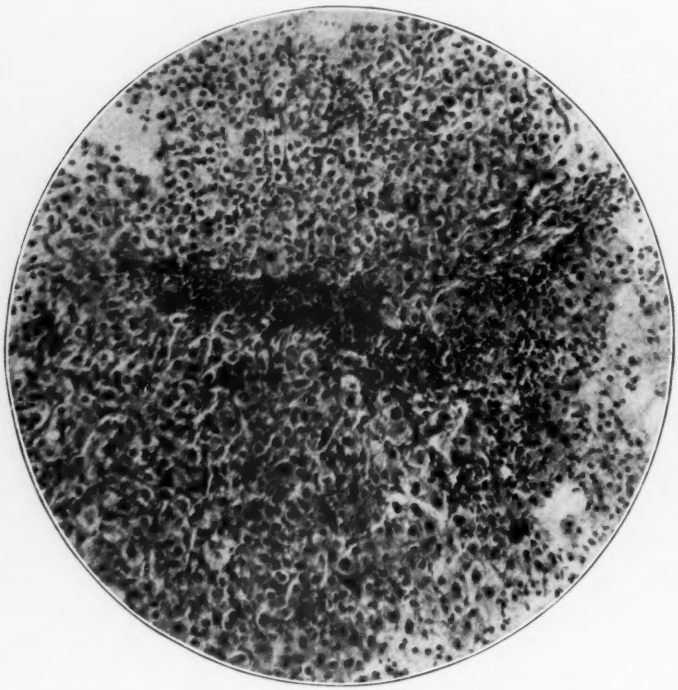

Fig. 8.—Biopsy specimen of the liver of a woman of 45 with subchronic atrophy of the liver, taken after one and three-quarters months' duration of symptoms. The duration of the disease to death was fourteen months.

In both groups of material, a few patients had perihepatitis as a sequela.

11. Snell, A. M.: Fundamentals in the Diagnosis of Jaundice, J. A. M. A. **138**:274-279 (Sept. 25) 1948.

12. Scheel, V.: Studies on Cholelithiasis, Ugesk. f. læger. **73**:1756-1774, 1911. Hansen, S.: Cholelithiasis, ibid. **84**:405-421, 1922. Wollesen, J. M.: Pregnancy and Gallstone Formation, Thesis, Copenhagen, 1940.

Microscopic Anatomy.—Biopsy of the liver was carried out according to the method of Iversen and Roholm [13] in 8 of the 108 cases of subchronic atrophy of the liver. Biopsy was undertaken after one, one and one-fourth, one and one-half, one and three-fourths, two, three, six and fourteen months of jaundice, respectively. The findings were the same in all instances and can be characterized as violent hepatitis (figs. 7, 8 and 9). The trabecular plan was indistinct. A number of the parenchyma

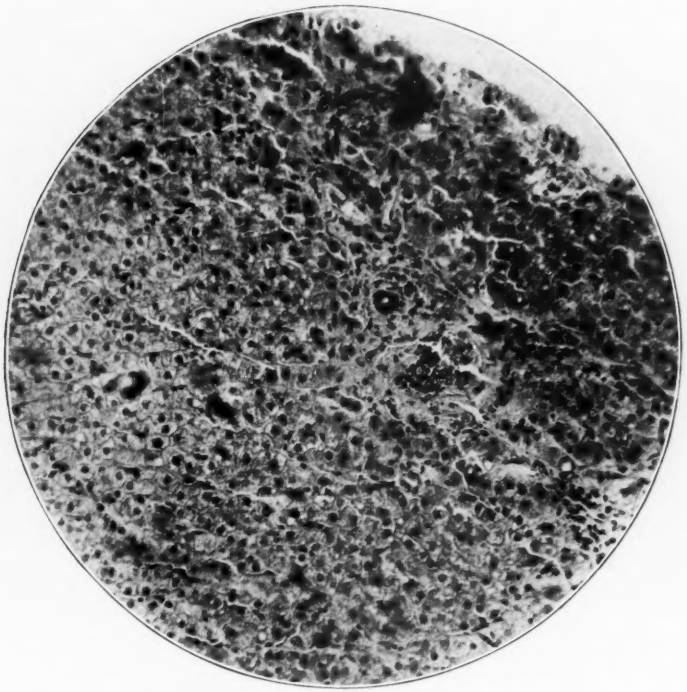

Fig. 9.—Biopsy specimen of the liver of a man of 36 with acute hepatitis, taken after two months duration of symptoms. A follow-up examination one month later showed no symptoms or signs of hepatic disease.

cells appeared strikingly large, with large nuclei. An intense infiltration of inflammatory cells was found in the periportal spaces, as well as interstitially in the parenchyma. The connective tissue in the periportal spaces was considerably increased in quantity. Bile pigment was found, mainly intracellularly, in the form of fine granules, but various accumu-

13. Iversen, P., and Roholm, K.: An Aspiration Biopsy of the Liver, with Remarks on Its Diagnostic Significance, Acta med. Scandinav. **102**:1-16, 1939.

lations of bile pigment were also found in the form of elongated globules. There was nothing in the microscopic appearance of the liver in the cases of subchronic atrophy of the liver which distinguished it fundamentally from that in the cases of severe acute hepatitis, but in no instance of benign hepatitis did we find such great changes (especially in connection with intralobular cell infiltration) at such a late stage after the inception of the disease (fig. 9).

Other Findings.—Icterus: By far the greater number of patients with subchronic atrophy of the liver died with icterus (94 of 105 patients, or 90 per cent), whereas only 11 patients died without icterus and had never had icterus at any stage of the hepatic disease. Compared with this figure, only 30 (41 per cent) of 74 patients with Laennec's cirrhosis had icterus at the time of death. This coincides with the fact that loss of hepatic function dominates the pathologic picture to a greater extent in subchronic atrophy of the liver than in Laennec's cirrhosis.

TABLE 1.—*Disorders in Cases Complicated with Ascites*

Disorder	Cases of Subchronic Atrophy of the Liver	Cases of Laennec's Cirrhosis
Esophageal varices	40 (50%)	29 (72.5%)
Splenic enlargement	44 (55%)	22 (55%)
Hydrothorax	39 (48.7%)	17 (42.5%)
Edema of the legs	48 (60%)	25 (62.5%)
Lumbar edema	37 (46.2%)	.....

As regards the degree of icterus there was also a difference, since one half of 94 patients having icterus together with subchronic atrophy of the liver had an icterus index (Meulengracht) above 40, whereas only one third of 30 patients with Laennec's cirrhosis had an index above 40 (the index was reckoned at the time of death).

Ascites: Ascites was found at the autopsies of 80 patients (74.1 per cent) with subchronic atrophy of the liver, whereas only 40 patients (54 per cent) with Laennec's cirrhosis had ascites. As regards the degree of ascites, the distribution among the patients was as follows: 8 (10 per cent) had less than 0.5 liter of fluid, 48 (60 per cent) had between 0.5 and 2 liters and 24 (30 per cent) had over 2 liters. The percentage distribution was the same among the patients with Laennec's cirrhosis.

It is apparent from table 1 how often patients with subchronic atrophy of the liver or Laennec's cirrhosis complicated with ascites had the following disorders at the time of autopsy: esophageal varices, splenic enlargement, hydrothorax and edema of the legs and of the lumbar region.

The cause of ascites in portal cirrhosis is generally considered to be partly portal hypertension and partly low colloid osmotic pressure.

This hypothesis was first presented by Iversen.[14] In an earlier study with Brun,[15] we investigated the colloid osmotic pressure in subchronic atrophy of the liver in order to determine the pathogenesis of ascites in this disease. We found that all patients with ascites and edema had a colloid osmotic pressure below 220 to 240 mm. of water, whereas those without ascites and edema had a higher colloid osmotic pressure. Since, in addition, ascites usually occurs at the same time as edema of the legs and since ascites may completely disappear, it was concluded that low colloid osmotic pressure was the most essential factor in the pathogenesis of ascites. It is still believed that low colloid osmotic pressure is the essential cause of ascites occurring in subchronic hepatitis. In this series, however, postmortem findings showed that esophageal varices also appeared in 50 per cent of the cases of subchronic atrophy of the liver with ascites. A certain degree of portal hypertension must therefore exist in this disease. A closer analysis of the figures shows that esphageal varices are more frequent in Laennec's cirrhosis, just as their degree of development is greater in this disease, as will be indicated. Thus there can be no doubt at all that portal hypertension is more developed in Laennec's cirrhosis than in subchronic atrophy of the liver.

Splenic Enlargement: Splenomegaly in the chronic diseases of the liver is thought, in general, to be caused by portal hypertension; McNee,[16] however, stated that the enlargement can arise on a toxic basis. The possibility that splenomegaly may be due to immunization processes must also be taken into consideration. Subchronic atrophy of the liver is presumably a virus infection, and the occurrence of splenomegaly in infectious diseases and experimental immunization is a well known phenomenon.[17]

In our postmortem material, of the subjects with subchronic atrophy of the liver 54 (50 per cent) had splenic enlargement, whereas it was not apparent in 54. Of the subjects with Laennec's cirrhosis, 56 per cent cent had splenic enlargement.

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14. Iversen, P.: Untersuchungen über die Ascitespathogenese, Klin. Wchnschr. **7**:2001-2004, 1928.

15. Bjørneboe, M.; Brun, C., and Raaschou, F.: Colloid Osmotic Pressure in Chronic Hepatitis, Arch. Int. Med. **83**:539-546 (May) 1949.

16. McNee, J. W.: Liver and Spleen: Their Clinical and Pathological Associations, Brit. M. J. **1**:1111-1116, 1932.

17. (*a*) Hellman, T., and White, G.: Das Verhalten des lymphatischen Gewebes während eines Immunisierungsprozesses, Virchows Arch. f. path. anat. **278**:221-257, 1930. (*b*) Rich. A. R.: Acute Splenic Tumor Produced by Non-Bacterial Antigens, Proc. Soc. Exper. Biol. & Med. **32**:1349-1351, 1935. (*c*) Bjørneboe, M., and Gormsen, H.: Experimental Studies on the Rôle of Plasma Cells as Antibody Producers, Acta path. et microbiol. Scandinav. **20**:649-692, 1943.

With regard to the degree of splenic enlargement observed at autopsy in subchronic atrophy of the liver, 33 subjects had a slight degree of splenic enlargement (the volume was greater than 12 by 8 by 4 cm.). Twenty had moderate splenic enlargement, the volume being greater than 15 by 10 by 6 cm., and only 1 patient had a large degree of splenic enlargement, with a volume greater than 20 by 12 by 8 cm. The distribution was the same in among the patients with Laennec's cirrhosis, which in itself is remarkable, since it is presumed from the foregoing data that portal hypertension is more developed in Laennec's cirrhosis.

Thirty-two of the 54 patients with splenic enlargement (51.8 per cent) did not have esophageal varices. This figure permits the assumption that there really are causes of splenic enlargement apart from portal hypertension. Splenic enlargement without esophageal varices appeared in only 24 per cent of the subjects with Laennec's cirrhosis; if one assumes that there are only the three aforementioned causes of spleno-

TABLE 2.—*Degree of Severity of Esophageal Varices*

Degree	Cases of Subchronic Atrophy of the Liver	Cases of Laennec's Cirrhosis
(+)	1 (2.1%)	1 (2%)
+	26 (54.2%)	16 (38%)
++	18 (37.5%)	15 (36%)
+++	3 (6.2%)	10 (24%)

megaly, splenic enlargement arising on a toxic or immunologic basis plays a smaller part in Laennec's cirrhosis than in subchronic atrophy of the liver.

Nearly all patients with subchronic atrophy of the liver and splenic enlargement had ascites at the same time (44 patients, or 81.5 per cent), whereas only 23 of 41 patients (56 per cent) with Laennec's cirrhosis had ascites at the same time as splenic enlargement.

Esophageal Varices: Esophageal varices were found in 48 subjects (44.4 per cent) with subchronic atrophy of the liver and in 42 (58 per cent) with Laennec's cirrhosis. Only 1 subject (0.9 per cent) with subchronic atrophy of the liver died after rupture of the varix with hematemesis, whereas 5 (6.6 per cent) with Laennec's cirrhosis died after rupture. This difference, too, indicates the greater degree of portal hypertension in patients with Laennec's cirrhosis, as do the figures in table 2, giving the degree of severity of esophageal varices for the two conditions.

Hydrothorax: The occurrence of hydrothorax in hepatic diseases is an argument for the existence and importance of low colloid osmotic

pressure if diseases of the heart, kidneys and lungs are excluded. Forty-two subjects (38.9 per cent) with subchronic atrophy of the liver and 24 subjects (32 per cent) with Laennec's cirrhosis had hydrothorax.

Of the 42 subjects with subchronic atrophy of the liver, 13 had unilateral and 29 bilateral hydrothorax. Twenty of these had under 0.5 liter of fluid, 21 between 0.5 and 1 liter and 1 over 1.0 liter. Of the subjects with Laennec's cirrhosis only one fifth had more than 0.5 liter. Thus, as regards the degree of hydrothorax, a considerable difference is to be found between the two diseases.

A pronounced correlation exists between the occurrence of hydrothorax and that of ascites and edema, which points to the fact that low colloid osmotic pressure is a cause of ascites and edema. Of 42 subjects with subchronic atrophy of the liver and hydrothorax, 40 (95.3 per cent) had ascites at the same time; the great majority of these (69 per cent) had edema of the legs.

Edema of the Legs and the Lumbar Region: Information about the occurrence of edema of the legs in subchronic atrophy of the liver was given in 98 instances. In 52 patients (53.1 per cent) edema of the legs was observed during hospitalization; 92.4 per cent of these had ascites and 55.8 per cent hydrothorax.

Lumbar edema was observed in 29 (41.9 per cent) of 93 patients in whom the symptoms had been observed. Of these, 94.5 per cent had ascites and 52.8 per cent hydrothorax. Similar figures were recorded for patients with Laennec's cirrhosis. These figures indicate a close connection between ascites and edema.

Hemorrhagic Diathesis: An indication of a tendency toward hemorrhage was found at autopsy in 70 patients (64.8 per cent) with subchronic atrophy of the liver. Localization occurred in the following organs, in order of decreasing frequency: the pleura (43 patients), the pericardium (32), the endometrium (25), the intestines (17), the skin (13), the endocardium (8), the nose (4), the ovaries (1), the meninges (1) and the bile ducts (1).

Twelve patients (16 per cent) with Laennec's cirrhosis had a hemorrhagic tendency; thus, there exists a distinct difference between the diseases in this particular.

Since the prothrombin concentration was decreased in all patients with subchronic atrophy of the liver and hemorrhagic tendency, it is reasonable to assume that the hemorrhages are due to the decreased production of prothrombin in the liver, which is another indication that hepatic insufficiency is far more pronounced in subchronic atrophy of the liver than in Laennec's cirrhosis.

Among other causes of hemorrhagic tendency in hepatic diseases, thrombopenia [18] must be mentioned and, especially so far as uterine hemorrhages are concerned, proliferation hemorrhage on the basis of the increased appearance of estrogens in the blood in cirrhosis of the liver.[19]

Disorders of the Gastrointestinal Tract: Gastric ulcer occurred in 11 (10.2 per cent) of the cases of subchronic atrophy of the liver. As a rule, completely fresh ulcers or erosive gastritis were concerned; in no case was there a chronic gastric ulcer. There is therefore little doubt that these gastric ulcers arise as a result of the disease of the liver. This connection has been suggested before, among other factors, by Schnitker and Hass.[20] In this series, with Laennec's cirrhosis 19 per cent of 72 patients had gastric ulcer.

Of all the patients with hepatitis, 9 died of hematemesis and melena; only 1 of these had rupture of esophageal varices, whereas bleeding from the stomach in the others was due to gastric ulcer. In 2 cases the source of hemorrhage could not be established at autopsy.

Among those with Laennec's cirrhosis only 2 patients (2.6 per cent) with gastric ulcer and hematemesis were observed and 2 with cancer of the stomach.

Lucké [7] mentioned that he found phlegmonous enteritis in the ileocecal part of the intestinal tract in 15 per cent of cases of acute yellow atrophy of the liver. There was no case with this complication in our epidemic.

Disorders of the Cerebrum [21]: The brain was examined microscopically in 8 cases of subchronic atrophy of the liver. In all edema of the brain was observed, and in 2 degeneration of the ganglion cells was noted. Lucké [7] observed similar edema of the brain in acute yellow atrophy of the liver and perivascular and meningeal lymphocytic infiltrations in 15 per cent of the patients in his series. Decourt, Bertrand, Guillaumin and Gruner [22] similarly stated the opinion that edema of the brain and degeneration of the ganglion cells play an important part in hepatic coma in acute yellow atrophy of the liver.

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18. King, R. B.: Blood Picture in Portal Cirrhosis of Liver: Report Based on One Hundred Cases, New England J. Med. **200**:482-484, 1929.

19. Biskind, M. S., and Biskind, S. R.: Effect of Vitamin B Complex Deficiency on Inactivation of Estrone in the Liver, Endocrinology **31**:109-114, 1942.

20. Schnitker, M. A., and Hass, V. G. M.: A Histological Study of the Liver in Patients Affected with Peptic Ulcer, Am. J. Digest. Dis. **1**:537-543, 1934.

21. Microscopic examinations of the brains were made by Dr. Erna Christensen.

22. Decourt, J.; Bertrand, I.; Guillaumin, C. D., and Gruner, J.: Ictère aigu apyrétique avec atrophie jaune aiguë du foie: Rôle de l'œdème cérébral dans la pathogénie du coma terminal, Bull. et. mém. Soc. méd. d. hôp. de Paris **62**:33-37, 1946.

These changes must be assumed to be the underlying pathoanatomic cause of the neurologic symptoms in the clinical picture. In our material the symptoms were characterized by semiconsciousness to a varying degree over a period of several days; no excitation or convulsions were noted.

Disorders of the Bone Marrow: Material was previously published by one of us on sternal punctures in 15 cases of chronic hepatitis,[23] data on some of which are included in the present material dealing with subchronic atrophy of the liver. The results are given in table 3.

The concentration of serum globulin was determined by the method of Henriques and Klausen.[24] The normal limits by this method are 1.7 to 3.1 Gm. per hundred cubic centimeters.[25] Gormsen [26] indicated that by far the largest number of normal persons have less than 1 per cent of plasma cells in the sternal marrow but that amounts up to 3 per cent can be seen under normal conditions. It can be deduced from the table that there is a tendency toward the increase of plasma cells in the sternal

TABLE 3.—*Concentration of Plasma Cells in Sternal Marrow and of Serum Globulin in 15 Cases of Chronic Hepatitis*

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Plasma cells, per cent of nucleated cells	4.5	4	4	3	3	3	2	2	2	2	2	2	2	1	1
Serum globulin, Gm./100 cc.	5.5	6.1	3.8	5.3	5.1	5.1	2.9	4.3	4.5	5.5	3.2	3.5	4.1	2.8	2

marrow among these patients, and that the concentration of serum globulin shows a tendency to become greater with the increasing quantity of plasma cells in the sternal marrow. This discovery was compared with the hypothesis put forward by Bjørneboe and Gormsen [17c] concerning the plasma cells as a place of production for the globulin of antibodies, and the opinion was formed that the investigations supported the view put forward previously,[27] namely, that the increase of serum globulin in hepatitis is connected with the formation of antibodies. Material on the basis of 24 sternal punctures undertaken in patients with chronic

23. Bjørneboe, M.: Serum Protein Variations in the Course of Chronic Hepatitis, Acta med. Scandinav. (supp. 206) **130**:392-398, 1948. Examinations of the sternal marrow were made by Dr. H. Gormsen.

24. Henriques, V., and Klausen U.: Untersuchungen über den Serumalbumin- und Serumglobulingehalt des Serums unter wechselnden Umständen, Biochem. Ztschr. **254**:414-433, 1934.

25. Bing, J.; Naeser, J.; Rasch, G., and Roejel, K.: Serum Proteins in Normal People, Acta med. Scandinav. **126**:351-369, 1946.

26. Gormsen, H.: Study of Bone Marrow, Thesis, Copenhagen, 1942. Physicochemical Properties of Blood: Changes in Serum Proteins; Reduction in Oxygen Saturation of Arterial Blood, Ann. Int. Med. **9**:690-711, 1935.

27. Snell, A. M.: Effects of Chronic Disease of Liver on Composition and Physicochemical Properties of Blood: Changes in Serum Proteins; Reduction in Oxygen Saturation of Arterial Blood, Ann. Int. Med. **9**:690-711, 1935.

hepatitis in the same epidemic [28] showed moderate hyperplasia of the marrow and a slight increase of plasma cells together with more or less pronounced erythroblastosis in a number of instances.

CLINICAL SURVEY

Subchronic Atrophy of the Liver.—The duration of disease was known in 98 cases (90.7 per cent of all the material). Far more of these patients than of those with Laennec's cirrhosis can as a rule give an account of the duration of the disease. On the average the duration was eight and two tenths months, the limits being one and thirty-two months (fig. 10). In 48 cases (49 per cent) the duration was under five months; in 21 (19.5 per cent), it was over one year.

The disease begins with a preicteric phase, with anorexia, nausea, vomiting, lassitude and sometimes arthralgias. Jersild [1b] showed that the preicteric phase is as a rule longer than in acute hepatitis.

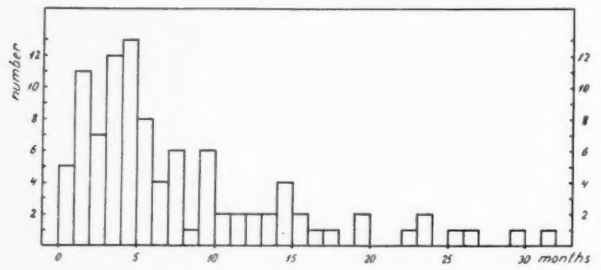

Fig. 10.—Duration of symptoms in subchronic atrophy of the liver.

The patients then become icteric. The icteric phase is characterized in this disease by a high icterus index and long duration. Often the icterus disappears, to recur later one or more times (in 55 cases there was 1 relapse; in 23, 2; in 9, 3, and in 5, more than 3). As a rule the patients die icteric; only 10 patients (10 per cent) had no icterus at autopsy. These patients had had icterus at no other time during the course of the disease.

Ascites is a frequent complication, appearing very late in the disease. With the presence of ascites the prognosis as a whole is extremely poor, though a few patients do improve.[29]

The duration of ascites was known in 49 cases (61.3 per cent) of those of subchronic atrophy of the liver. The duration was: 26 cases,

28. Meulengracht, E., and Gormsen, H.: Blood and Bone Marrow in Infective Subacute and Chronic Atrophy of the Liver, Blood **3**:1416-1425, 1948.

29. Bjørneboe, M.: Serum Protein Variations in Chronic Hepatitis and the Clinical Course of the Disease, Acta med. Scandinav. **132**:170-180, 1948.

less than one month; 13, less than two; 5, less than three, and 5, more than three.

A relatively large number of patients with subchronic atrophy of the liver had at one time or another pains in the epigastrium or in the right upper quadrant of the abdomen. Of 80 patients for whom information about this symptom was available, 36 (45 per cent) had pain. The existence of pains was not related to the observance of the sequela of perihepatitis.

The clinical picture is also characterized by anorexia and lassitude. Edema of the legs and the lumbar region frequently occurs with ascites. Sooner or later signs of hemorrhagic tendency arise and finally semiconsciousness, developing into coma.

Laboratory tests have shown that as a rule in this disease there are positive reactions to the Takata-Ara test [30] and the thymol turbidity test [31] and low serum albumin and high serum globulin,[29] together with decreased prothrombin concentration in the blood, which is unaffected by the injection of water-soluble vitamin K preparations.[1a] In a number of cases there has been an increase of iron in the blood serum,[18] decreased colloid osmotic pressure in the blood when ascites is present,[15] moderate anemia, often with an increase in the diameter of erythrocytes and a tendency toward leukopenia.[28]

Causes of Death: Nearly all patients with subchronic atrophy of the liver died of loss of hepatic function with hepatic coma. Nine patients, as already mentioned, died of hematemesis and melena, 15 with pneumonia as a complication and 6 of other causes (hemiplegia, barbiturate poisoning, acute pancreatic necrosis and complications following cholecystectomy and gastric resection).

We have attempted to relate the frequency of hepatic coma in subchronic atrophy of the liver and Laennec's cirrhosis with the "volume index of the liver" which was calculated as indicated previously. It is apparent from figure 6 that the volume index in subchronic atrophy of the liver always lies below 3,000, whereas only 63 per cent of the patients with Laennec's cirrhosis had a volume index below 3,000. Hepatic coma appears, as already mentioned, as the cause of death of practically all patients with subchronic atrophy of the liver, whereas at most 43 per cent of the patients with Laennec's cirrhosis died of hepatic coma. It can be seen from figure 6 that hepatic coma occurs mainly in the patients having the lowest volume index of the liver.

According to these data, it is presumably legitimate to relate small hepatic volume and hepatic coma; moreover, the relation appears to be fairly obvious.

30. Footnote 1, *a*, *b* and *c*.

31. Marner, I. L.: The Thymol Reaction as a Liver Test, Acta med. Scandinav. **131**:180-192, 1948.

No relation was found between the duration of symptoms and the volume index of the liver in subchronic atrophy of the liver.

Laennec's Cirrhosis.—Evidence of previous syphilis was found in 16 per cent of these patients; the corresponding figure for those with subchronic atrophy of the liver was 2.8 per cent. Alcoholism was observed in 8 per cent. None of the patients with subchronic atrophy of the liver was addicted to alcohol. Former icterus (i. e., at least a year before the first symptom of hepatic cirrhosis) was noted in 6 cases (8 per cent), whereas none of the patients with subchronic atrophy of the liver had had icterus previously. This figure must certainly be taken as a minimum, since the case records were often incomplete on these points. An indication can be seen, however, of the well known fact that syphilis and alcoholism are found relatively often among patients with cirrhosis of the liver. On this point, subchronic atrophy of the liver seems to differ from Laennec's cirrhosis.

The duration of symptoms was evident in only 44 (58 per cent) of the cases of Laennec's cirrhosis as against 90.7 per cent of those of subchronic atrophy of the liver; the information offered was in many cases uncertain. It is characteristically difficult to determine the time of onset of the disease in Laennec's cirrhosis, in contrast to subchronic atrophy of the liver. In 23 cases (30 per cent) the duration of symptoms was under five months; in 7 (9.2 per cent) it was over twelve months. Thus, no striking difference in the duration of symptoms was discovered, even though among the cases of Laennec's cirrhosis there were relatively more with a duration of symptoms of five to twelve months. There was information about the first symptom in 44 (58 per cent) of the cases. In order of descending frequency, the first symptoms were as follows: icterus, ascites, lassitude, dyspepsia, edema, pains in the region of the liver, diarrhea and hematemesis. Ten patients (9 women and 1 man) occupied an exceptional position in regard to symptoms, since the course of their illness corresponded completely to that of subchronic atrophy of the liver. When these patients are not included in the material a different order is obtained in the symptoms mentioned, namely, ascites, edema, lassitude, dyspepsia, icterus, pains, diarrhea and hematemesis. This order in regard to frequency corresponds more closely with what is generally indicated in the literature on the subject.[32]

32. The distribution according to sex shows, as in other material in Laennec's cirrhosis, a preponderance of men. It is not especially marked, however. As has already been mentioned, 10 patients occupied a special position in having a course of symptoms as in subchronic atrophy of the liver. If these patients are not included in the material a sex distribution of 24 women and 42 men is obtained, more closely related to the sex distribution of other series and to that of the material from previous years from Kommunchospitalet (fig. 4).

The 10 patients with Laennec's cirrhosis already mentioned, who clinically presented the appearance of subchronic atrophy of the liver, had symptoms the duration of which did not differ fundamentally from the duration of symptoms in subchronic atrophy of the liver (5 patients, less than five months; 3 patients, more than twelve months). Thus, we were not able in our material to find a basis for the assumption previously advanced [33] that specially prolonged cases of subchronic atrophy of the liver present the appearance of Laennec's cirrhosis pathoanatomically.

As mentioned previously, 40 (54 per cent) of the subjects had ascites when the autopsy was made. The duration was determined for only 21, of whom 7 had ascites less than one month; 6, less than two months; 4, less than three months, and 4, more than three months. On this point there was no difference in the two types of material. In Laennec's cirrhosis the occurrence of ascites is a very bad sign for prognosis, as is well known.

In 20 cases there was evidence of pains in the epigastrium or in the right upper quadrant. This number represents scarcely half the cases in which the symptom was known to exist. In this factor there was no difference in the two types of materials.

Causes of Death: Of the patients with Laennec's cirrhosis, at most 33 (43 per cent) died of hepatic coma, as previously mentioned. It has already been stated that this is a considerably lower frequency than in subchronic atrophy of the liver. In 9 cases the diagnosis of coma was uncertain; in 8 of these an infection was found at the same time, and the death of the ninth patient was in connection with a cholecystectomy.

The other causes of death were as follows: bleeding from esophageal varices, 5 patients; bleeding from gastric ulcer, 2; primary cancer of the liver, 5; portal thrombosis, 2; cardiac insufficiency, 8; cancer with different localizations, 6; resection for cancer of the stomach, 2; pneumonia, 4, and different causes, 9. In the last group the causes were the following: nephritis with uremia, tumor of the spinal cord, cholecystectomy complicated with peritonitis, fracture of the femur, fracture of the skull, cerebral hemorrhage and pulmonary embolism (1 patient each) and prostatic hypertrophy with pyelonephritis (2 patients).

Heart diseases in the material will be dealt with more closely. As already indicated, 8 patients died of cardiac insufficiency. The frequency of pathologic conditions of the heart was, however, much greater. When the milder variations, such as a slight degree of coronary arteriosclerosis, cardiac hypertrophy or sequels to endocarditis, were disregarded the figures in table 4 were obtained.

33. Faber, M.: Note on Porto-Caval Anastomoses, Ugesk. f. læger. **108**:928 1946.

In all, 46 patients (61 per cent) of the 76 with Laennec's cirrhosis were found to have these variations. This was a considerably higher frequency than in the cases of subchronic atrophy of the liver, in which the following variations were observed.

These variations were noted in 30 subjects in all (28 per cent). The most striking difference in the two groups of material with regard to these changes is the difference in the occurrence of cardiac hypertrophy, which is connected with the fact, established by Raaschou,[34] that there are strikingly few patients with arterial hypertension among

TABLE 4.—*Pathoanatomic Changes in the Heart in Laennec's Cirrhosis*

Change	No. of Cases
Cardiac hypertrophy	19
Coronary arteriosclerosis	25
Occlusion of the coronary artery	2
Mitral stenosis	2
Aortic stenosis	1
Pericardial adhesions	4
Acute pericarditis	4
Subacute endocarditis	1
Syphilitic aortitis	3
Myocardial fibrosis	1

TABLE 5.—*Pathoanatomic Changes in the Heart in Subchronic Atrophy of the Liver*

Change	No. of Cases
Cardiac hypertrophy	2
Coronary arteriosclerosis	25
Occlusion of the coronary artery	1
Sequel to mitral endocarditis	1
Pericardial adhesions	1
Myocardial fibrosis	2

those with subchronic atrophy of the liver. Among the subjects with Laennec's cirrhosis, one third had arterial hypertension (as indicated by a systolic blood pressure of over 150), a figure which corresponds with normal findings in postmortem material within these age ranges.[34]

On the whole, the impression was gained that the causes of death in the subjects with Laennec's cirrhosis were distributed, as might have been expected, among a set of people in this age group. The impression was also given that only in a minority (especially those with the smallest livers) was hepatic disease a direct cause of death through hepatic coma, rupture of esophageal varices or portal thrombosis. Corresponding to

34. Raaschou, F.: Blood Pressure and Heart Weight in Chronic Hepatitis, Nord. med. **42**:1791-1795, 1949.

this, the diagnosis in subchronic atrophy of the liver is nearly always made during life, while only in 23 (29 per cent) of the cases of Laennec's cirrhosis was cirrhosis suspected before autopsy.

COMPARISON OF SUBCHRONIC ATROPHY OF THE LIVER AND LAENNEC'S CIRRHOSIS

The differences, apart from the appearance of the liver, in the pathologic picture and the clinical aspect of subchronic atrophy of the liver and Laennec's cirrhosis may be briefly summarized:

1. Nearly all patients with subchronic atrophy of the liver are women, whereas there is a preponderance of men as far as Laennec's cirrhosis is concerned.

2. The impression is obtained that portal hypertension is more pronounced in Laennec's cirrhosis than in subchronic atrophy of the liver, since the esophageal varices are more frequent and more pronounced in Laennec's cirrhosis, just as the frequency of rupture of the varices is greater in this disease.

3. It is our opinion that the low colloid osmotic pressure dominates the clinical picture more in subchronic atrophy of the liver than in Laennec's cirrhosis, since the frequency of ascites and the degree of hydrothorax found at autopsy are greater in subchronic atrophy of the liver than in Laennec's cirrhosis.

4. Pronounced impairment of hepatic function is more frequent in subchronic atrophy of the liver, as may be seen from the fact that hemorrhagic tendency and death from hepatic coma are far more frequent in this disease than in Laennec's cirrhosis.

The size of the liver, expressed as its volume index, is on the average smaller in subchronic atrophy of the liver than in Laennec's cirrhosis, which presumably is the cause of the greater frequency of hepatic coma in the former. The frequency of hepatic coma is greater in subjects with Laennec's cirrhosis with a low volume index than in those with a high volume index, which also supports this assumption.

5. In addition, the following factors are allied with these differences: 1. A greater frequency of syphilis, alcoholism and icterus in anamnesis (i. e., more than a year before the first symptom) occurs in Laennec's cirrhosis. 2. Gallstones and heart disease (especially cardiac hypertrophy) occur in greater frequency in Laennec's cirrhosis (primary carcinoma of the liver and hepatomas do not occur at all in subchronic atrophy of the liver, in contrast to Laennec's cirrhosis). 3. In the great majority of cases of subchronic atrophy of the liver evidence as to the duration of symptoms can be obtained from the patient, whereas this happens far less often in Laennec's cirrhosis. 4. Laennec's cirrhosis was not diagnosed during life in three quarters of the cases,

but since 90 per cent of patients with subchronic atrophy of the liver have jaundice during life this condition can usually be recognized clinically as a hepatic disease. 5. The frequency and degree of enlargement of the spleen are identical in subchronic atrophy of the liver and Laennec's cirrhosis. However, there are more cases of enlargement of the spleen without esophageal varices in subchronic atrophy of the liver. To sum up, one may state that subchronic atrophy of the liver leads to a greater degree of reduction of the liver parenchyma than does Laennec's cirrhosis. From the clinical point of view, a greater frequency of symptoms of loss of hepatic function and a greater frequency of death from hepatic coma are in accord with this conclusion.

SUMMARY

The cases of subchronic atrophy of the liver described in the literature up to the time of writing have been chiefly isolated cases appearing in case materials of acute yellow atrophy of the liver.

The present work is based on autopsy material consisting of 108 cases of subchronic atrophy of the liver and 76 cases of Laennec's cirrhosis.

Material.—Subchronic Atrophy of the Liver: The material consisted of 108 subjects (6 men and 102 women) on whom autopsy was undertaken from Jan. 1, 1944 to Jan. 1, 1948. Practically all the patients died after their fortieth year.

Laennec's Cirrhosis: The material consisted of 76 subjects (43 men and 33 women). The age range corresponded to that in subchronic atrophy of the liver.

Frequency: An examination of the collected postmortem material at Kommunehospitalet from 1928 to 1947 inclusive showed that the number of cases of Laennec's cirrhosis was more or less constant, whereas instances of subchronic atrophy of the liver appeared only sporadically before 1944.

Pathologic Anatomy.—The macroscopic and microscopic pathologic anatomy of the disease is described according to the literature.

The microscopic anatomy of the liver on biopsy corresponded to that of acute hepatitis of severe degree.

The weight of the liver in most cases was found to be reduced to below half the normal weight.

A fairly exact correlation was found between the weight of the liver and the volume index of the liver (determined by multiplication of the three dimensions).

The volume index of the liver in subchronic atrophy of the liver showed a smaller variation than that in Laennec's cirrhosis. The reduction of the liver parenchyma was generally more pronounced in subchronic atrophy of the liver.

Icterus appeared in 90 per cent of the patients with subchronic atrophy of the liver at the time of death, whereas 10 per cent died without icterus and without having had icterus at any stage of the disease. Only 41 per cent of the patients with Laennec's cirrhosis had icterus at the time of death.

Ascites occurred in 74.1 per cent of the patients with subchronic atrophy of the liver and in 54 per cent of those with Laennec's cirrhosis. No difference in the degree of ascites was observed in the two diseases.

The pathogenesis of ascites is discussed, and it is emphasized that the reduced colloid osmotic pressure is regarded as the dominant factor in subchronic atrophy of the liver. The occurrence of mild esophageal varices in half the cases, however, indicated that slight portal hypertension also occurs in this disease.

Enlargement of the spleen was a symptom which appeared with equal frequency (in about half the cases) in these diseases; the degree of enlargement of the spleen was also identical. Enlargement of the spleen without esophageal varices was somewhat more frequent in subchronic atrophy of the liver, which is expressive of the fact that enlargement of the spleen arising on a toxic or immunologic basis may possibly play a greater part in this disease than in Laennec's cirrhosis.

Esophageal varices were found in 44.4 per cent of the subjects with subchronic atrophy of the liver and in 58 per cent of the subjects with Laennec's cirrhosis. In the latter disease they were more pronounced. This, together with the more frequent occurrence of rupture of varices in Laennec's cirrhosis, indicated that portal hypertension is more pronounced in the latter disease.

Hydrothorax was of almost equal frequency at the time of death in the two diseases (it occurred in 38.9 per cent of the subjects with subchronic atrophy of the liver and in 32 per cent of those with Laennec's cirrhosis). Greater degrees of pleural effusion were found in subchronic atrophy of the liver than in Laennec's cirrhosis. In subchronic atrophy of the liver there is a pronounced correlation between the occurrence of hydrothorax and that of ascites and edema, which supports the assumption that low colloid osmotic pressure is a cause of ascites and edema.

Edema of the legs was found at death to be of equal frequency in these diseases (it occurred in at least half the cases).

A hemorrhagic tendency was observed far oftener in subchronic atrophy of the liver than in Laennec's cirrhosis (in 64.8 per cent of the subjects as against 16 per cent). This difference in frequency is related to the reduced prothrombin content of the blood and to the more frequent occurrence of loss of hepatic function in subchronic atrophy of the liver.

Gastric ulcer was found in 10.2 per cent of subjects with subchronic atrophy of the liver and in 2.6 per cent of those with Laennec's cirrhosis. In many instances the ulcers bled and caused hematemesis and melena.

In the microscopic examination of the brain in subchronic atrophy of the liver, cerebral edema and, in some cases, degeneration of the ganglion cells were discovered.

When the sternal marrow was examined, a slight tendency toward increase was observed in the plasma cells.

Hepatomas and primary carcinoma of the liver were not found at all in the subjects with subchronic atrophy of the liver, whereas they appeared in some with Laennec's cirrhosis.

Gallstones appeared less often in subchronic atrophy of the liver than in Laennec's cirrhosis.

Clinical Aspects.—Subchronic Atrophy of the Liver: The duration of the symptoms in the present series was on the average eight and two tenths months, varying from one to thirty-two months. The course of the disease is characterized by a long preicteric period and by an icteric phase which consists of several waves of icterus in succession (in 37 cases there was more than 1 relapse of icterus in the course of the disease). Ascites occurs late in the disease. In more than half the cases in which evidence was given of the duration of ascites, there was at most one month between the occurrence of ascites and death. Pains in the epigastric region or in the right upper quadrant were noted in barely half the cases. Edema occurred as a rule at the same time as ascites; sooner or later a hemorrhagic tendency appeared, and finally semiconsciousness developed into coma. Nearly all the patients forming the material died of hepatic coma (9 died of hematemesis and melena, 15 with complicating pneumonia and 6 of other causes). The frequent occurrence of hepatic coma and of small volume index of the liver are related to each other.

Laennec's Cirrhosis: Syphilis, alcoholism and previous icterus (occurring more than one year before the first symptom) were more frequent in anamnesis among patients with Laennec's cirrhosis than among those with subchronic atrophy of the liver. Evidence as to duration of the disease was given less often by patients with Laennec's cirrhosis than by those with subchronic atrophy of the liver. In the cases in which such evidence was given, there was no certain difference in the duration of symptoms between the two types of material. The initial symptoms were as follows, in order of decreasing frequency: icterus, ascites, lassitude, dyspepsia, edema, pains in the region of the liver, diarrhea and hematemesis. In Laennec's cirrhosis there was a short interval between the occurrence of acites and death. Pains in the region of the liver were noted with the same frequency as in the material for subchronic atrophy of the liver—in almost half of

the cases. The cause of death was hepatic coma in 33 cases (43 per cent); in 9 of these, however, the diagnosis of coma was uncertain. The instances of coma occurred mainly among patients with a small volume index of the liver, which observation strengthens the assumption that it is the reduction in quantity of hepatic cells which causes the loss of hepatic function. The remaining causes were distributed over a series of different diseases characteristic for the age groups included in the material. There was a pronounced difference in the frequency of hypertrophy of the heart in the two groups of material. In Laennec's cirrhosis hypertrophy of the heart was observed in one quarter of the subjects, whereas it was observed in only 2 of the 108 subjects with subacute atrophy of the liver. This circumstance was presumably due to the fact that arterial hypertension is remarkably rare in patients with subacute atrophy of the liver.

To sum up, it can be stated that subacute atrophy of the liver leads to a greater degree of reduction of the liver parenchyma than does Laennec's cirrhosis. Clinically a greater frequency of symptoms of loss of hepatic function is in accord with this, as is a greater frequency of death from hepatic coma.

ANEMIA ASSOCIATED WITH CIRRHOSIS OF THE LIVER

Study of Thirty-Two Cases

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MACROCYTIC anemia associated with cirrhosis of the liver has been repeatedly observed in Western countries. Assuming that the function of the liver plays a part in normal erythropoiesis, Van Duyn [1b] stated the belief that the pathologic changes in that organ might be held indirectly responsible for the development of the macrocytic blood picture. Davidson and Fullerton [2] suggested that the macrocytic anemias of hepatic disease are caused by failure of the final stages of synthesis of the hemopoietic principle rather than by failure to store the substance.

Goldhamer and his associates [3] observed that an extract prepared post mortem from the liver of a patient with cirrhosis and macrocytic anemia was ineffective in eliciting a hemopoietic response when administered parenterally to a patient with pernicious anemia in relapse. This observation with other experimental data led them to conclude that the specific hemopoietic substance might not be stored by a severely damaged liver or, even though stored, might not be delivered to the tissues.

Offering contrary evidence was the work of Schiff and his associates,[4] who prepared extracts from the livers obtained post mortem from 5 patients with clinical hepatic disease. There were 2 patients with portal cirrhosis, 1 with obstructive cirrhosis secondary to neoplasm of the hepatic duct, 1 with chronic passive congestion and 1 with extensive leukemic infiltration. The extracts were administered intramuscu-

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1. (*a*) Babonneix, L., and Tixier, L.: Gaz. méd. de Nantes **31**:681, 1913. (*b*) Van Duyn, J. V.: Macrocytic Anemia in Disease of the Liver, Arch. Int. Med. **52**: 839 (Dec.) 1933. (*c*) Gamma, C.: Minerva med. **6**:797, 1926. (*d*) Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923, pp. 321, 304, 320 and 350. (*e*) Remen, L.: Med. Klin. **28**:514, 1923.

2. Davidson, L. S. P., and Fullerton, H. W.: Quart. J. Med. **7**:43, 1938.

3. Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: Am. J. M. Sc. **188**:193, 1934.

4. Schiff, L.; Rich, M. L., and Simon, S. D.: Am. J. M. Sc. **196**:313, 1938.

larly to a suitably controlled group of patients with pernicious anemia in relapse. Characteristic reticulocytosis resulted, followed by an increase in hemoglobin concentration and in red cell count and by marked clinical improvement. The 3 patients with cirrhosis had macrocytic anemia, whereas the type of anemia in the remaining 2 cases was not definitely determined. The authors therefore concluded that the human liver may contain the specific hemopoietic principle even when it is the seat of extensive and protracted disease. This holds true even in the presence of macrocytic anemia, strongly suggesting that the macrocytic anemia associated with hepatic disease is not caused by failure of the liver to store the specific antianemic substance.

The fact that hepatic damage may be associated with macrocytic anemia is established; yet, the question of the mechanism of macrocytosis is still not settled at the time of writing. In China, cirrhosis of the liver is rather common. It is hoped that this study of the anemia associated with the disease may throw some light on the macrocytosis.

MATERIAL AND METHODS

The material consisted of 32 cases of typical cirrhosis of the liver, diagnosis in 4 of which was verified by biopsy. The hemoglobin concentration was determined with Sahli's hemometer; the red corpuscle count, with the improved Neubauer bright line hemacytometer; the hematocrit reading, by Wintrobe's method, and the mean corpuscular diameter by the direct measurement method of Price-Jones on 500 corpuscles. Sternal puncture was performed in 19 cases to determine the presence of the megaloblasts of Ehrlich.

DATA

The anemia in all cases was of the normocytic type except in 2 (case 4 and case 32), in which there was macrocytosis with a mean corpuscular volume of 112 and 114 cubic microns, respectively, and a mean corpuscular diameter of 8.023 and 8.461 microns, respectively. In none of the 2 cases of macrocytic anemia or the 17 in which a sternal puncture was made was the presence of a typical megaloblast observed, but in case 4 the presence of hyperplastic normoblasts was determined. The details are presented in the accompanying table.

COMMENT

Since the improved morphologic study of the red corpuscles developed, anemia has been classified into normocytic, microcytic and macrocytic types. Whenever the mean corpuscular volume in a case of anemia is found to be greater than 94 cubic microns, the disease is macrocytic.[5] The cause is usually one of the following: (1) lack of intake of the extrinsic factor of Castle, as in tropical macrocytic anemia; (2) absence of the intrinsic factor of Castle, as in typical pernicious

5. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 4. Philadelphia, P. Blakiston's Son & Co., 1944, p. 1450.

Summary of Thirty-Two Cases of Cirrhosis of the Liver Associated with Anemia

No.	Age, Yr.	Sex	Evidence of Cirrhosis of Liver	Blood Data												
				Red Blood Cells, Millions/ Cu. Mm.	Hemoglobin Value, Gm./ 100 Cc.	White Blood Cells, per Cu. Mm.	Hematocrit Reading, Percentage	Mean Corpuscular Volume, Cu. u	Mean Corpuscular Hemoglobin, Micromicrograms	Mean Corpuscular Hemoglobin Concentration, Percentage	Price-Jones Curve: Mean Corpuscular Diameter u	Price-Jones Curve: Standard Deviation u	Price-Jones Curve: Variation, Percentage	Sternal Marrow: Megaloblasts	Sternal Marrow: Leukocyte: Erythrocytic Ratio
1	32	M	Ascites; enlarged spleen; dilated abdominal veins	2.15	5.0	1,960	18.0	84.0	23.5	28.0	7.264	0.990	13.5	—	32:68
2	67	M	Ascites; enlarged spleen	2.31	7.7	7,000	....	....	33.0	....	7.562	0.984	13.0	—	.....
3	54	M	Ascites; enlarged spleen; jaundice	3.45	9.8	4,200	33.0	95.6	28.7	29.7	7.006	0.756	9.9	—	40:60
4	54	M	Ascites; enlarged spleen; dilated abdominal veins	2.22	8.4	.....	25.0	112.0	37.0	33.6	8.023	0.848	10.6	—; hyperplastic normoblasts	53:47
5	28	M	Ascites; enlarged spleen; dilated abdominal veins	2.58	7.5	.....	23.6	91.0	29.3	32.0	7.831	0.899	11.5	—	.....
6	59	F	Ascites; enlarged liver and spleen; dilated abdominal veins	3.62	10.2	.....	33.3	90.2	28.0	30.5	7.401	0.782	10.3	..	.....
7	25	M	Ascites; enlarged liver and spleen; dilated abdominal veins	4.39	12.5	.....	35.0	80.4	28.7	36.0	.....	.....	....	..	.....
8	45	M	Ascites; enlarged spleen; dilated abdominal veins	3.17	9.9	6,400	31.0	97.8	31.3	31.8	7.718	1.190	15.4	—	65:35
9	32	M	Ascites; enlarged spleen; dilated abdominal veins	3.60	12.6	.....	33.0	91.6	30.0	33.0	.....	.....	....	—	68:32
10	14	M	Persistently enlarged liver and spleen	2.82	7.3	.....	28.0	99.0	25.7	25.8	7.563	0.970	12.6	—	49:51
11	30	M	Jaundice; ascites; dilated abdominal veins	3.73	12.3	.....	32.0	95.0	31.2	38.0	7.733	0.750	10.2	—	.....
12	24	M	Ascites; enlarged spleen; dilated abdominal veins; cirrhosis proved by biopsy	3.63	10.9	.....	31.5	86.8	30.0	34.0	6.868	0.803	11.6	—	45:55
13	27	M	Ascites; dilated abdominal veins; jaundice	2.25	4.1	.....	22.2	99.0	19.0	19.0	7.518	1.038	13.8	..	.....
14	44	M	Ascites; enlarged spleen; dilated abdominal veins	3.15	7.6	.....	27.6	97.6	24.1	27.0	6.916	0.810	11.7	..	.....
15	27	M	Ascites; enlarged spleen; cirrhosis proved by biopsy	2.76	8.8	3,000	23.0	84.0	31.7	38.0	7.477	0.810	10.8	—	.....
16	46	F	Ascites; enlarged spleen; dilated abdominal veins; hematemesis	....	...	.....	....	....	....	....	6.716	0.886	13.2	—	61:39
17	42	M	Ascites; enlarged spleen; dilated abdominal veins	3.30	9.2	.....	25.0	75.8	27.8	36.6	7.520	0.810	10.8	—	50:50
18	35	M	Ascites; enlarged spleen; dilated abdominal veins; hematemesis	2.38	7.7	.....	22.0	94.5	32.3	35.0	7.598	0.830	10.9	..	.....
19	65	M	Ascites; enlarged liver and spleen; dilated abdominal veins	3.10	10.5	4,000	28.0	90.0	33.9	37.5	7.846	0.421	5.3	..	.....
20	42	F	Persistently enlarged spleen	2.58	7.0	.....	26.0	100.8	27.0	26.9	7.783	1.006	12.9	—	.....
21	57	F	Biliary cirrhosis discovered during cholecystectomy	3.70	12.5	.....	35.0	95.0	34.0	36.0	7.348	0.717	9.8	..	.....
22	40	M	Ascites; enlarged spleen; dilated abdominal veins	3.50	10.5	.....	23.3	92.3	30.0	32.0	7.148	0.921	12.9	—	60:40
23	29	M	Ascites; enlarged spleen; dilated abdominal veins	3.63	13.0	.....	35.0	96.0	31.5	32.0	7.519	0.749	9.8	..	.....
24	24	M	Ascites; enlarged spleen; dilated abdominal veins; hematemesis; jaundice	3.74	11.9	.....	34.5	91.4	31.8	34.5	7.721	0.900	11.0	..	.....
25	22	M	Ascites; enlarged spleen; dilated abdominal veins; jaundice	3.80	10.9	.....	36.0	94.7	28.6	30.2	7.096	0.880	11.4	..	.....
26	27	M	Enlarged spleen	3.39	10.5	.....	32.0	74.4	30.9	32.8	7.673	0.910	12.0	..	.....
27	24	M	Ascites; enlarged spleen	3.40	9.8	.....	28.5	83.8	28.8	34.4	7.557	0.673	8.9	—	46:54
28	44	M	Progressively enlarged liver and spleen; jaundice; ascites	....	...	.....	....	....	....	....	7.461	1.000	13.0	..	.....
29	34	M	Ascites; dilated abdominal veins	3.51	11.2	.....	32.0	91.1	31.8	38.0	7.706	0.650	8.8	..	.....
30	29	F	Jaundice; enlarged liver and spleen; early cirrhosis proved by biopsy	3.24	10.5	.....	31.0	96.0	32.1	33.9	7.841	0.800	11.0	—	67:33
31	28	M	Ascites; enlarged spleen; dilated abdominal veins	2.80	7.5	.....	26.0	92.9	26.9	28.1	7.652	0.770	10.0	—	68:32
32	22	M	Ascites; jaundice; hematemesis	3.33	11.4	.....	38.0	114.0	37.1	30.0	8.461	0.860	11.5	—	70:30

anemia; (3) poor absorption of the hemopoietic principle, as in idiopathic steatorrhea; (4) poor storage of the principle in the liver, as in cirrhosis of the liver, or (5) lack of utilization of the principle, as in the achrestic anemia of Israels and Wilkinson.[6] In short, all macrocytic anemias are supposed to be due to one single cause, that is, deficiency of the hemopoietic principle.

Recent developments, however, suggest that not all macrocytic anemias are caused by such a deficiency. According to this concept, two types may be distinguished:

One is the megaloblastic type, which is due to deficiency of the hemopoietic principle. This deficiency results in abnormal erythropoiesis which gives rise to the production of megaloblasts of Ehrlich (partly or completely hemoglobinized cells two to four times the size of an ordinary normocyte, the nuclei of which, though larger than those of normoblasts, do not occupy so much of the cell area, are finely reticulated and stain faintly[7]) and, in turn, to macrocytosis. With liver therapy the megaloblastic hemopoiesis gives way to normoblastic hemopoiesis, and the anemia and macrocytosis subside. The diagnosis of this type of anemia should be based on the presence of macrocytosis and of megaloblasts in the bone marrow and the peripheral blood, and on a good response to liver therapy.

The other type is the macrocytic anemia occurring in severe hemolysis, certain types of aplastic anemia or diseases of the liver in which there is hyperplasia of the hemopoietic tissue evidenced by the presence of hyperplastic normoblasts, as described by Zanaty[8] and Israels.[9] These are large cells, but never equal in size to the megaloblasts; their nuclei occupy most of the cell area, and the maturation of the nuclei always precedes that of the cytoplasm; namely, the cells undergo pyknosis before complete hemoglobinization of the cytoplasm occurs, whereas the nuclei in megaloblasts are always less mature than the cytoplasm. The presence of these cells in the bone marrow does not indicate a deficiency of the hemopoietic principle but an increased demand on the normal hemopoietic tissue, which, in response to the call, puts out the hyperplastic normoblasts, which results in a slight or moderate degree of macrocytosis. This macrocytic anemia is not improved by liver therapy.

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6. Israels, M. C., and Wilkinson, J. F.: Quart. J. Med. **5**:69, 1936.

7. (*a*) Israels, M. C. G.: J. Path. & Bact. **49**:231, 1939. (*b*) Jones, O. P., in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2061. (*c*) Schulten, H.: Die Sternalpunktion als diagnostische Methode, Leipzig, Georg Thieme, 1937, p. 39. (*d*) Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942, p. 63.

8. Zanaty, A. F.: Lancet **2**:1365, 1937.

9. Israels, M. C. G.: Lancet **2**:207, 1941.

It is not easy to make a distinction between a megaloblast and a hyperplastic normoblast, the latter frequently having been taken for a megaloblast. For instance, Janet M. Vaughan [10] took such a hyperplastic normoblast, observed in a case of leukoerythroblastic anemia, to be a megaloblast. The close scrutiny of one smear, kindly given us by her, convinced us that the large cells were not megaloblasts. We also saw 2 patients with these cells. One had extremely severe, fatal macrocytic anemia of the aplastic type, due to the toxic effect of sulfonamide drugs and neoarsphenamine, which showed no response to the administration of iron or liver. The other had Marchiafava-Micheli syndrome with macrocytosis which showed no definite response to liver therapy, but there was a spontaneous remission. At first, we took these cells to be megaloblasts, but having read recent articles on them we believe they are hyperplastic normoblasts.

Although the distinction is sometimes difficult, the separation of these two types of macrocytic anemia (megaloblastic and hyperplastic) is of practical value, for it clears away a good deal of confusion in hematology and helps one to understand better the mechanism of macrocytosis. For instance, Hill and Hausmann,[11] in 1943, reported a case of macrocytic anemia secondary to acute hepatitis and supposed to have been cured by liver extract. Casual reading may convince one that that case supports the view that hepatitis causes deprivation of the hemopoietic principle and gives rise to megaloblastic anemia which responds to the administration of liver extract. The authors did not, however, determine the mean corpuscular volume of the red cells, though the color index was 1.37; they neglected the significance of the absence of megaloblasts of Ehrlich in the sternal marrow and of the slow response to the administration of liver extract (it took fifty-two days to raise the red cell count from 2,300,000 to 4,400,000 with liver extract). These facts plus the knowledge of two types of macrocytic anemia make us skeptical about the relation between this anemia and the deficiency of the hemopoietic principle. Appreciating the difference between the two types, Zanaty [8] stated the belief that achrestic anemia is a special form of aplastic anemia in which there is hyperplasia of the bone marrow, resulting in the production of large normoblasts, and that, of course, that type of macrocytic anemia does not respond to liver extract.

Our 32 patients all had normocytic anemia except 2, who had macrocytic anemia but without the presence of megaloblasts in the marrow. One of them, however, had hyperplastic normoblasts in the

10. Vaughan, J. M.: The Anaemias, ed. 2, New York, Oxford University Press, 1936, p. 139, plate 3, opposite p. 158.

11. Hill, J. N., and Hausmann, W.: Brit. M. J. **2**:262, 1943.

marrow. These cases strongly suggest that deficiency of the hemopoietic principle is not of significance in the anemias associated with cirrhosis of the liver, for there would likely have been at least a few cases of megaloblastic anemia among the 32 should cirrhotic change interfere with the storage of the hemopoietic principle.

Wintrobe,[12] in his book on "Clinical Hematology," states: "While it is undoubtedly true that cirrhosis of the liver and pernicious anemia may sometimes occur in the same individual, this explanation cannot account for the majority of the cases of macrocytic anemia under discussion [macrocytic anemia associated with disease of the liver]." We quite agree with his view. We believe that some examples of macrocytic anemia associated with cirrhosis of the liver in Western countries are of the megaloblastic type, that is, due to a lack of the hemopoietic principle, and that they occur coincidentally with, but not as a result of, the damage to the liver, because we do not see such megaloblastic anemia associated with cirrhosis of the liver in China, where pernicious anemia is exceedingly rare [13] and the anemia associated with the cirrhosis occurs in its uncomplicated form. The other instances of macrocytic anemia associated with cirrhosis are the result of hyperplasia of the bone marrow, as exhibited in our 2 cases. The cause for such hyperplastic erythropoiesis is not yet known. Heinle and others [14] stated the belief that increased destruction of blood may play a role in the anemia of liver cirrhosis, and Tsai and his associates [15] showed that congestion of the spleen causes increased fragility of the red cells.

In all cases of cirrhosis of the liver, the spleen is continuously much congested; it would be logical to conclude that anemia associated with cirrhosis is probably due to increased destruction of blood in the much congested spleen, which process perhaps does result in the majority of cases of normocytic and normochromic anemia. In a small percentage, however, in which the destruction is much exaggerated and the demand on the bone marrow is naturally intensified, the marrow may become hyperplastic and produce the large cells to make the anemia macrocytic. A correlation between the degree of macrocytosis and the size of the spleen would be of interest.

Our observation may explain the apparent discrepancy between the report by Goldhamer and his associates [8] on a case of cirrhosis of the liver associated with macrocytic anemia, in which the liver was proved to contain no hemopoietic principle, and a report by Schiff and his

12. Wintrobe, 7d, p. 318.

13. One of us (K-w H.) has seen only 1 patient with typical megaloblastic anemia during eight years' clinical experience in Chengtu. Snapper, I.: Chinese Lessons to Western Medicine, New York, Interscience Publishers, Inc., 1941, p. 264.

14. Heinle, R. W.; Gastle, W. B., and Rose, F. A.: Folia haemat. **64**:174, 1940.

15. Tsai, C.; Lee, J. S., and Wu, H.: Chinese J. Physiol. **15**:165, 1940.

associates [4] on cases of hepatic disease, in which the liver was proved to have stored the principle satisfactorily. No doubt, the case of Goldhamer and his co-workers was one of cirrhosis complicated by pernicious anemia in relapse, and the liver, of course, contained no such principle, whereas the cases of Schiff and his associates were probably uncomplicated examples of hepatic diseases, in which the liver, as in our 32 cases, did not fail to store the principle.

Therefore, one may conclude that damage to the liver, as in cirrhosis, probably does not interfere with the function of storage of the hemopoietic principle or with the final stage of its synthesis, because it does not give rise to megaloblastic anemia and because the liver has been proved to have stored the principle satisfactorily.[4] Anemia occurring with cirrhosis of the liver is of the normocytic type in the majority of cases, but occasionally it is macrocytic, of the hyperplastic type. The mechanism is not clear, but stasis of a great amount of blood in the enlarged spleen may cause increased destruction of blood and thereby may bring about a normocytic anemia; when the process is intensified, hyperplasia of the bone marrow may result in macrocytosis.

SUMMARY AND CONCLUSION

Thirty-two cases of cirrhosis of the liver associated with anemia were studied hematologically. The anemia in all cases was found to be normocytic except in 2, in both of which it was macrocytic, in 1 of which the presence of the so-called hyperplastic normoblasts was established in the marrow and in none of which megaloblastic erythropoiesis was observed.

The pathogenesis of macrocytosis associated with cirrhosis of the liver is discussed.

Chronic damage to the liver as it occurs in cirrhosis probably does not interfere with the proper storage of the hemopoietic principle or with the final stage of its synthesis and therefore does not give rise to megaloblastic anemia.

DEVELOPMENT OF PORPHYRIA IN DIABETES MELLITUS

Report of Three Cases

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SINCE Gunther's original description of acute porphyria as a clinical entity was published in 1911, a number of reviews [1] have appeared on the subject. Although porphyria and porphyrinuria have been associated with many toxic states and with other disease entities,[1a,f] the only reference in the literature to an association of acute porphyria with diabetes mellitus seems to be the statement, ". . . it has also been found in diabetes mellitus," appearing in the section on porphyria in Duncan's textbook.[2]

At the Albert Merritt Billings Hospital there are, at the time of this report, records of a total of 8 proved cases of acute porphyria, in 3 of which the diagnosis of diabetes mellitus was also substantiated. In each case, the diabetes had been present for some years before symptoms of porphyria appeared.

The apparently complete dissociation of pigment metabolism and carbohydrate metabolism makes it difficult to suggest an explanation for the curious concomitance of these two metabolic disorders.

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1. (*a*) Dobriner, K., and Rhoads, C. P.: The Porphyrins in Health and Disease, Physiol. Rev. **20**:416-468, 1940. (*b*) Mason, V. R.; Courville, C., and Ziskind, E.: Porphyrins in Human Disease, Medicine **12**:355-439, 1933. (*c*) Nesbitt, S., and Watkins, C. H.: Acute Porphyria, Am. J. M. Sc. **203**:74-83, 1942. (*d*) Waldenström, J.: Some Observations on Acute Porphyria and Other Conditions with a Change in the Excretion of Porphyrins, Acta. med. Scandinav. **83**:281-316, 1934; (*e*) Studien über Porphyria, ibid., 1937, supp. 82, pp. 1-254. (*f*) Watson, C. J.: The Porphyrins and Their Relation to Disease, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 4, pt. 2, p. 228.

2. Duncan, G. G.: Diseases of Metabolism, ed. 2, Philadelphia, W. B. Saunders Company, 1947.

REPORT OF CASES

CASE 1.—*First Admission.*—M. G., a man, married, a real estate agent aged 34, on entering the hospital had had paralysis of the arms and legs for two months.

History: Three years before admission the patient had noted the onset of weakness and fatigue, with a loss of weight of 60 pounds (27 Kg.) in three months. A physician found complete reduction of copper in the urine and diagnosed diabetes mellitus. There had been no polydipsia, polyuria or polyphagia. After four months' trial on a diet the patient was given protamine zinc insulin, 30 to 35 units daily. Glycosuria was fairly well controlled, and the patient was normally active. The patient's father was known to have had diabetes for ten years, but there was no other family history of the disease.

Four months before admission the patient took a long bus trip during which insulin was omitted for two days. He became ill and was admitted to a hospital in acidosis, which was treated with fluids intravenously and large amounts of insulin. During his stay, paraldehyde sedation was given. In a week he was discharged as improved.

On his return home his wife, who tested his urine, noted a reddish coloration of the urine which was almost continuous, though varying in degree. After three days at home severe weakness, headache, nausea and vomiting developed and the patient was readmitted in coma, in which state he was said to have remained for several days in spite of the administration of large amounts of insulin. Subsequently the level of blood glucose was said to have dropped abruptly to 27 mg. per hundred cubic centimeters, at which time the patient's legs and arms felt numb and he was almost unable to move them, although he retained good strength in the fingers and toes. There was aphonia, but at times he could speak in a faint whisper. For several days he was incontinent in feces and urine. Examination of the spinal fluid showed only a positive response to the Pandy test. The patient was discharged but bedridden after six weeks, subsequently recovering enough motor power to sit up sometimes, but during the eight weeks before the first admission to the Albert Merritt Billings Hospital he was too weak to clear the mucus from his mouth and he complained of needle-like pains in the extremities. For two weeks he had nausea, vomiting, diarrhea and chills, and during the four days prior to admission he was again incontinent of feces.

During the ten years prior to admission there had been exposure to lead paint when the patient worked as a building supervisor.

Physical Examination: The temperature was 98 F. and the pulse rate 130, and there were 28 respirations per minute. The patient was an emaciated young adult man, unable to move his extremities, appearing acutely ill and breathing rapidly. He could not speak or swallow and had no control over the sphincters of the bladder or rectum. The ophthalmoscopic examination was noncontributory. The skin was warm and moist. There was dulness over the lung bases with many moist rales. The heart was not enlarged, but the rate was rapid and the sounds were distant. The pulse was weak. The blood pressure was 90 systolic and 50 diastolic. The edge of the liver and the tip of the spleen were felt on deep inspiration. The genitalia were normal, and the rectal examination was noncontributory. There was some edema of the dorsal surfaces of the feet. The extremities were markedly wasted and showed flaccid paralysis, with weak hand grasp and absence of reflexes. The vibratory sense was absent. A pinprick was discerned only as a "numb" feeling over the extremities.

Laboratory Examination: The urine was often dark reddish brown and gave a positive response to the test with Ehrlich's aldehyde reagent in dilutions as high as 1:256. The specific gravity ranged up to 1.025. Glycosuria was usually

minimal but sometimes severe, and there was occasional acetonuria. A twenty-four hour specimen of the urine contained 0.011 mg. of lead. There were many white blood cells, and Aerobacter aerogenes was cultured; both the pyuria and the bacilluria cleared after sulfonamide therapy. Hematologic examinations gave normal results except for leukocytosis of 28,000 to 32,000 cells per cubic millimeter, with 86 per cent polymorphonuclear leukocytes; the leukocyte count was subsequently 12,000 to 15,000. The basal metabolic rate was minus 5. Roentgenograms of the chest and gallbladder were normal. Three examinations of the spinal fluid were noncontributory. The stools showed occasional occult blood. The values for blood sugar were occasionally above 200 mg. per hundred cubic centimeters, once reaching 364 mg. and a few times falling to hypoglycemic levels. The levels for serum carbon dioxide and chlorides were normal, as was the p_H, and the level for cholesterol was 210 mg. per hundred cubic centimeters. The concentration of plasma proteins was 6.40 Gm. per hundred cubic centimeters, with hypoalbuminemia (3.26 Gm.) and hyperglobulinemia (3.14 Gm.).

Course: This first admission, of ten months' duration, was marked by irrationality, abdominal pain, insulin reactions and convulsions in the earlier weeks and, subsequently, gradual improvement of the peripheral neuritis to a point where the patient could walk with a "walker." There was frequent paresthesia of the limbs. During more than half his stay the patient had a low grade intermittent fever with moderate leukocytosis; later this diminished somewhat. He exhibited periods of unresponsiveness and had bizarre hallucinations and delusions such as "awaking in a pool of blood," "having a brain in my back," etc. The diabetes was difficult to manage. Alimentation proved a major problem, requiring tube feeding for long periods. As the neurologic condition improved, the diabetes was controlled fairly well with 30 units of protamine zinc insulin and 15 units of crystalline zinc insulin each morning and 5 units of crystalline zinc insulin before supper. There were a number of episodes of agonizing abdominal pain, and toward the middle of this admission, prior to the identification of porphyrins in the urine, the patient underwent laparotomy and appendectomy during which extreme hypermotility of the ileum and colon was observed.

Excess urinary porphyrins were demonstrated by red fluorescence in ultraviolet light after ether extraction of the urine and confirmed by spectroscopic examination. After porphyrins were found in the urine, barbiturates were withheld. The patient received brewers' yeast, wheat germ oil, vitamin B preparations and injections of crude liver extract solution® and was treated by physical therapy. In the ensuing months, marked clinical improvement occurred, with a gain in strength, increased rationality and cessation of the abdominal pain. After discharge, the patient's motor power improved with the same regimen and he continued physical therapy at home, where he walked with crutches.

Second Admission.—On readmission a year later, the patient was ambulatory with help. He had generalized muscular weakness and atrophy, most pronounced at the distal joints (especially of the legs) but much less severe than before. The biceps and triceps reflexes were fairly active, the patellar reflexes weak and the ankle jerks absent. Sensation was normal in the arms, but there was a distal stocking hypalgesia and hypesthesia, with absence of the vibratory sense in the ankles. Porphyrins were again demonstrated in the urine, and the patient had another attack of acute abdominal pain. After discharge he had a "right-sided convulsion," after which the right arm and leg became weaker than the left and he fed himself with the left hand. There was a recurrence of progressive weakness, and there were episodes of agonizing pain in the abdomen and back.

Third Admission.—The patient was admitted for the third time two years after the first entry, with flaccid quadriparesis, distal paralysis, areflexia and hyperalgesia over the feet and legs and hypalgesia over the hands. There were irrationality, delusions and hallucinations, including "having four eyes," seeing the late President Roosevelt in the room, etc. Again porphyrins were demonstrated in the urine. Subsequently there was again improvement in motor power, and eventually the patient became able to walk without help. For two years, during which he was not followed, there was no redness of the urine or abdominal pain.

Fourth Admission.—The patient's final admission, for what was thought to be tuberculosis with cavitation of the upper lobe of the right lung, was preceded by six months of cough and hemoptysis during which time he did not seek medical attention. Previous roentgenograms had shown the chest normal. Pneumothorax, performed elsewhere, had not achieved satisfactory collapse and there was subsequent rupture of an adhesion, with hydropneumothorax, followed by empyema with hemolytic Staphylococcus aureus. Fluid of a dirty brown color reaccumulated after numerous thoracenteses. Tubercle bacilli were never demonstrated in the sputum or the pleural fluid. Terminally, oliguria occurred and the diabetes was out of control. The level of blood urea nitrogen rose to 59 mg. per hundred cubic centimeters. The level of serum phosphorus was 7.3 mg. per hundred cubic centimeters and that of serum calcium 7.2 mg. The patient died during a clonic convulsion. During this admission, porphyrins and porphobilinogen were intermittently present in the urine.

Diagnoses.—A clinical diagnosis of porphyria and diabetes mellitus was made, and the following conditions were diagnosed at autopsy: pyopneumothorax of the right side with chronic interstitial pneumonitis, massive atelectasis of the right lung, compensatory emphysema of the left lung, chronic fibrous pleuritis of the right side, fine fibrous adhesions of the left apical region, ulcerative esophagitis, mild chronic pyelonephritis, decubitus ulcers in the left gluteal region and absence of the appendix.

Chemical Study.—The study (by Dr. H. Klüver) of various organs, tissues and body fluids revealed large amounts of various ether-soluble and ether-insoluble porphyrins, partly in the form of the zinc complex. Further details will appear in another paper.

CASE 2.—H. S., a white man, an executive aged 53, with diabetes mellitus of five years' duration, entered the hospital with the complaints of anorexia, loss of weight and dyspnea.

History.—The diabetes had been regulated by diet alone until five months before admission when, because of a fasting blood sugar level of 150 mg. per hundred cubic centimeters, the patient had been given 30 units of protamine zinc insulin each morning. This was discontinued seven weeks later because of lower blood sugar levels. Four months before admission, after having had several teeth extracted and having been given poorly fitting dentures, the patient had experienced the onset of loss of appetite, weakness and moderate exertional dyspnea, all progressive up to the time of admission and accompanied by a 60 pound (27 Kg.) loss of weight. Two weeks before admission he noted increased prominence of the veins of the forehead and intermittent darkness of the urine. There was no edema of the ankles and no abdominal pain. He had been taking pentobarbital sodium (nembutal®) each night and at the time of admission was taking 3 grains (0.19 Gm.) of seconal sodium® each night because of insomnia. The past history was significant in that he had had syphilis at 16; the disease was treated with "hip shots" for three years, at which time the response to serologic tests became

negative. Tests of the blood and spinal fluid since the termination of treatment had been consistently normal. Five years before admission, during exercise, the patient had been seized with severe precordial pain that radiated to the left arm and persisted, gradually diminishing in severity, until the following morning. Two years before admission, while the patient was hospitalized elsewhere for weight reduction, a sudden severe pain developed in his neck. An electrocardiogram at that time was said to have revealed a myocardial infarction, and he spent the subsequent six weeks in bed. There was no history of angina pectoris. The family history revealed that the patient's mother had died at 59 of diabetes mellitus and nephritis, 3 sisters had died of cancer and 1 brother had disease of the coronary arteries.

Physical Examination.—The temperature was 36.2 C. (97.2 F.), the pulse rate was 100 and there were 20 respirations per minute. The patient was a gray-haired, middle-aged man with evidence of marked recent weight loss, appearing chronically ill but in no acute distress. There were 4 teeth remaining. The chest was emphysematous in form. A few inspiratory rales were heard at the base of the lungs. The heart was slightly enlarged to the left, with a gallop rhythm. The blood pressure was 150 systolic and 90 diastolic. The liver was palpaple in the right upper quadrant, but the edge was not clearly felt. The neurologic examination was normal. Numerous small subcutaneous nodules were palpable over the abdominal wall. The circulation times were prolonged. Proctoscopy was noncontributory.

Laboratory Examination.—On the patient's admission the hemoglobin concentration was 16.5 Gm. per hundred cubic centimeters; the red cell count was 5,500,000, and the white cell count, 12,650. The urine was orange-red in color, having a specific gravity of 1.034, a 1 plus value for albumin, no reduction of Benedict's solution, no acetone and a 2 plus reaction to Ehrlich's test for urobilinogen. Subsequently the test for porphobilinogen by the aldehyde reaction was positive; hence, it was assumed that porphobilinogen was mistaken for urobilinogen. The reaction to the Kahn test for syphilis was negative on two occasions. Specimens of the stools were negative for occult blood. The basal metabolic rates were minus 19 and minus 5. A gastric analysis revealed free acid after the administration of histamine. Roentgenographic studies showed a normal gallbladder, esophagus, stomach, duodenum and colon. A roentgenogram of the chest revealed an enlarged heart (70 per cent oversize) and moderate basilar pulmonary congestion. An electrocardiagram showed strain of the left ventricle and an intraventricular conduction defect. Chemical studies of the blood showed the following values: glucose concentration, 135 to 203 mg. per hundred cubic centimeters; nonprotein nitrogen, 25 mg.; serum carbon dioxide, 31.7 millimols per liter; serum p_H, 7.41; serum chlorides, 101 milliequivalents; serum cholesterol, 335 mg., and esters, 253 mg.; alkaline phosphatase, 5.1 Bodansky units; serum bilirubin, 0.3 mg. (direct), and 0.5 mg. (total), and total plasma proteins, 6.42 Gm. (albumin, 4.04 Gm., and globulin, 2.38 Gm.). The reaction to the thymol flocculation test was negative, and the value for cephalin flocculation was 1 plus. The value for the urea clearance test of Van Slyke was 54 cc. per minute, using the square root formula.

Course.—Throughout the patient's twenty-three day hospital stay, glycosuria was minimal or absent on a 1,650 calorie diet with 150 Gm. of carbohydrate and no insulin. Because of the persistence of symptoms involving the chest, the patient was digitalized beginning on the nineteenth hospital day. He complained bitterly of insomnia, for which he received various combinations of pentobarbital sodium, phenobarbital and amobarbital sodium (amytal sodium®) for the first fifteen days.

Fair sedation was eventually obtained with a combination of whisky and chloral hydrate. Increased salivation was a prominent symptom. The urine remained persistently a dark orange to an orange-red color. On several occasions it was found by the aldehyde test [1e] to contain porphobilinogen. Exposure to ultraviolet rays after ether extraction indicated excess porphyrins on one occasion. At no time did the patient complain of abdominal pain. No neurologic abnormalities were demonstrated, and no psychotic behavior occurred. He had three to five bowel movements each day.

After discharge, the patient was followed in the outpatient clinic for six months, after which he did not return. During that time, his urine remained dark in color. On one occasion he was thought to show peculiar behavior. He continued to have three to five bowel movements each day, and severe insomnia persisted in spite of the reinstitution of barbiturates.

Final Impression.—The final impression was that this was a case of porphyria, diabetes mellitus and arteriosclerotic heart disease.

CASE 3.—*First Admission.*—S. A., a housewife of 57, entered with pain and tenderness of two years' duration in the right upper quadrant of the abdomen and the right lower portion of the chest and complaining of a ten day exacerbation with intractable vomiting.

History: The patient had considerable difficulty with the language, which made the taking of a history unsatisfactory. She had been known to have diabetes for twenty years; the condition had been satisfactorily controlled with 10 units of protamine zinc insulin daily. Twenty years previously she had had gonococcal inflammatory disease of the pelvis and had undergone a pelvic operation. Approximately ten years previously she had had empyema of the right side, which had been treated by aspiration. Three years before her admission to this hospital an emergency operation had been performed for a strangulated hernia of the right femoral canal.

The patient's chief complaint dated back two years before admission, when she noted the onset of episodes of pain in the right upper quadrant of the abdomen, in the right lower portion of the chest and in the back, sometimes associated with vomiting. At times she suffered pain in the right shoulder, with or without radiation down the right arm. The latter pains sometimes occurred independently, and at other times in association with the pain in the right upper quadrant and in the right lower portion of the chest. The patient had had one or more episodes of cystitis, during which she was treated by her physician. Two months before this admission the pains in the right lower portion of the chest and in the abdomen became increasingly severe, with nausea and vomiting, and she entered another hospital. Roentgenograms of the gallbladder and retrograde pyelograms were normal. A neurologic consultant considered the pain "hysterical" in origin. After discharge the patient was no better and continued to have similar episodes. Ten days before admission to the Albert Merritt Billings Hospital there was exacerbation of the pain with paroxysms of vomiting and nausea. The pain apparently was worse and more frequent after meals, and the patient vomited all solid foods. In the clinic and on admission there was acetone in the urine, with only minimal glucose or none.

Physical Examination: The temperature was 36.6 C. (97.9 F.), the pulse rate was 88 and there were 20 respirations per minute. The patient was a well developed, fairly well nourished, elderly white woman who appeared depressed and rather chronically ill. She was restless, complaining of the pain as has been indicated. The skin and lymph nodes were normal. An ophthalmoscopic

examination showed a widened arteriolar light reflex, tortuosity of the arterioles and arteriovenous compression with scattered punctate hemorrhages and small, white, circumscribed exudates. The head, ears, nose, mouth, neck, breasts, chest and heart were not remarkable. The blood pressure was 120 systolic and 78 diastolic. Examination of the abdomen revealed pronounced tenderness in the right upper quadrant even on gentle palpation, and there was tenderness over the right lower portion of the chest and at the right costovertebral angle. The edge of the liver was felt 1 to 2 fingerbreadths below the right costal margin on inspiration. There were incisional scars on the right thigh and in the right suprapubic region. A neurologic examination was noncontributory.

Laboratory Examination: On admission of the patient the urine reduced Benedict's solution (1 plus) and contained acetone (1 plus). Later the same day there was no sugar but the acetone reaction was 4 plus. (During the latter part of the patient's course the glycosuria varied from 0 to 1 or 2 plus.) The urine was normal in color at all times. The aldehyde test [3] showed no porphobilinogen, but further tests for porphyrins were not carried out during this admission. Microscopic examinations of the sediment during the first days of the patient's stay revealed 15 to 50 white blood cells per high power field. Escherichia coli was cultured on two occasions; the infection cleared on sulfadiazine therapy. Hematologic examinations, the Kahn test and examinations of the stools gave normal results. A gastric analysis showed no free acid in the fasting specimen and 54 units of free acid fifty minutes after the administration of histamine. Tests of liver function gave normal results. Blood sugar was occasionally above 200 mg. per hundred cubic centimeters. Roentgenograms revealed the gallbladder, stomach, small intestine, colon and renal pelves to be normal. Splenic calcifications were observed. A roentgenogram of the chest showed nothing remarkable except calcification in the aortic arch and the major bronchi; there were minimal osteoarthritic changes in the thoracic portion of the spine. Fluoroscopic examination of the chest showed adequate motion of the diaphragm. Electrocardiograms disclosed right axis deviation with a prolonged QRS complex (0.12 seconds) and deep Q waves in leads II and III, interpreted on serial tracings as indicating a high grade intraventricular conduction defect and possible infarction of the posterior portion of the myocardium.

Course: The starvation ketosis present on the day of admission was promptly remedied by hypodermoclyses of dextrose and isotonic sodium chloride solution. The diabetes was satisfactorily controlled with globin insulin with zinc (20 units daily). The pains continued, occurring sometimes at irregular intervals but often after meals, which made feeding somewhat difficult. Toward the latter part of the patient's thirty-one day stay in the hospital, she felt somewhat better and was discharged, being able to take food well and to walk haltingly.

On her return home she did well for a week, although the pain persisted. It then became much severer, radiating up into the right side of the chest and the right shoulder almost constantly in the last three days before the second admission, at which time there were repeated emeses. She was brought back to the hospital agitated, making facial grimaces and drooling foamy saliva.

Second Admission.—During this admission the patient exhibited considerable fluctuation in the severity of the pain, which sometimes seemed to be relieved with sterile hypodermic injections. For a while there was hemihyperalgesia of the entire right side, but no other abnormal neurologic signs were observed.

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3. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. **47**:393-394, 1941.

At the beginning of the third week large amounts of porphyrins were found in the urine by exposure to ultraviolet light and spectroscopic examination after extraction with ether and acetic acid.[4] The urine remained normal in color, however, even when left exposed to sunlight for two weeks. Despite the presence of porphyrins, the aldehyde test [3] showed no porphobilinogen in the urine at any time. Subsequently all barbiturates were withheld without evident change in the clinical course.

At the end of the third week the patient had a brief episode of panic in which she left the bed and wandered down the corridor. When found she was cyanotic and was grimacing and blowing through her teeth. She expressed paranoid ideas, thinking that one of the interns was trying to kill her and that she had telephoned her husband. On her being put back to bed, the cyanosis subsided. Thereafter she had no similar episodes but retained her ideas about the imagined events.

During the third week there were dyspnea, tachycardia and basilar pulmonary rales and the liver was enlarged 8 cm. below the right costal margin. The patient gained weight progressively. A roentgenogram of the chest showed a small pleural effusion and increased bronchovascular markings. Considerable improvement followed digitalization, the intravenous administration of mercurophylline injection (mercuzanthin®) and aminophylline and the administration of ammonium chloride and a salt-poor diet. There was diuresis with a loss of 5 Kg. of body weight. Subsequently there was considerable improvement in the patient's general appearance with less frequent emeses, though she still complained of constant pain in the right portion of the thorax and in the right upper quadrant of the abdomen. The diabetes was finally controlled with 20 units of protamine zinc insulin and 5 units of crystalline zinc insulin every morning. While the patient had maximal pains her insulin requirement was higher (up to 30 units of protamine zinc insulin and 10 units of crystalline zinc insulin). During days of severe pain, twenty-four hour urine specimens contained up to 37 Gm. of glucose.

When the patient's condition appeared stable, she was discharged and went home to the care of her private physician. During the succeeding four months the patient was followed in the clinic. She continued to complain of abdominal pain in the right upper quadrant, especially after eating, and there were frequent rather severe attacks with facial grimacing and crying out. Triple bromide tablets and glyceryl trinitrate were said to have afforded some relief. There was occasional nocturnal dyspnea.

Third Admission.—Three days before the third admission the patient fell down at home, striking her head. There was a small amount of bleeding from the scalp. The pain became worse. She was confused, had dizzy spells, was unable to stand, complained of dyspnea and was admitted as an emergency patient.

The examination showed swelling over the right parietal region but no evidence of laceration or fracture. On this occasion the lungs were clear and the heart was not enlarged to percussion, but there was now a harsh apical systolic murmur transmitted to the left axillary region. The liver was felt 2 fingerbreadths below the right costal margin. There was tenderness to a light touch all over the abdomen.

As on the second admission, urinary porphyrins were demonstrated by fluorescence in ultraviolet light after extraction with ether and acetic acid, but they were present in smaller amounts than previously. The urine was again of normal color and no porphobilinogen was demonstrated by the aldehyde test.

4. de Langen, C. D., and ten Berg, J. A.: Porphyrin in the Urine as a First Symptom of Lead Poisoning, Acta med. Scandinav. **130**:37-44, 1948.

The serum bromide level was 219 mg. per hundred cubic centimeters, and sodium chloride was given.

After initial improvement in the patient's mental state, she suddenly became weak on the evening of the third day. The extremities were cold, the pulse was faint and the blood pressure was unobtainable. The urine showed a small amount of glucose. She was given 25 Gm. of glucose intravenously without effect. An electrocardiogram was unsatisfactory because of twitching movements as the patient lapsed into coma, but Wenckebach's periods were discernible in lead I. After brief tonic and clonic convulsions the heart sounds became irregular and the patient died.

Diagnoses.—Porphyria and diabetes mellitus were the clinical diagnoses. The following were determined at autopsy: extreme arteriosclerosis of all organic arteries, especially the coronary arteries; old occlusion of the right coronary artery and healed infarction of the posterior portion of the left ventricle; arteriosclerotic obliteration of the coronary arteries, recent occlusion of the left coronary artery at its bifurcation and infarction of the entire (?) left ventricle; pulmonary edema and hyperemia; hydrothorax of the left side and fibrous obliteration of the right pleural space; arteriosclerotic atrophy of the brain; arteriosclerotic scarring of the cortex of the kidneys; atrophy of the tail of the pancreas and hyalinization of the islets of Langerhans; fatty infiltration of the liver; acute splenic hyperplasia (cause undetermined); recent superficial occipital contusion, and chronic endocervicitis and absence of the ovaries, the fallopian tubes and the body of the uterus (a healed surgical incision was noted).

COMMENT

In all 3 cases here reported, diabetes antedated the first symptoms or observations suggesting the presence of porphyria.

The first patient had diabetes of three years' standing before the sudden onset of porphyria, characterized by generalized paresis and dark-colored urine. At the time of onset the patient was hospitalized elsewhere for the treatment of acidosis; it is known that he received large amounts of insulin and was at one time in severe hypoglycemia. He was said to have received large amounts of paraldehyde. Whether barbiturates or sulfonamide drugs were administered at that time could not be determined, but under our observation the withdrawal of all barbiturates was followed by rather pronounced clinical improvement. The patient was, however, receiving large doses of crude liver extract solution® as well as other medicaments during that time. The patient had had contact with lead paints over a period of several years, although not immediately preceding the onset of paresis. Since the urinary excretion of lead was found to be well within normal limits,[5] plumbism as a cause of the porphyrinuria [6] in this case can be discounted. Prior to the diagnosis of porphyria, the possibility of diabetic polyneuritis had

5. Goodman, L., and Gilman, A.: The Pharmocological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, The Macmillan Company, 1941, p. 723.

6. de Langen and ten Berg.[4] Waldenström.[1d]

been considered by some of the physicians who saw the patient. It is worthy of note that at laparotomy extreme intestinal hyperperistalsis was observed. (Gastric atony and diminished peristaltic sounds were described by Berg,[7] whereas severe gastrointestinal spasm was described by Prunty.[8])

The second patient had had diabetes for five years before the passage of dark urine was noted. The prolonged use of barbiturates preceded the onset of porphyrinuria in this case. Excess urinary excretion of porphyrins was repeatedly demonstrated, but none of the usual clinical manifestations of acute porphyria was observed except intractable insomnia.

In case 3, the patient had had diabetes for twenty years before the onset of abdominal pain. As the psychic and neurologic manifestations became more severe, a steady rise in the insulin requirement took place in spite of diminished carbohydrate intake.

In none of the cases were quantitative studies or qualitative extraction with identification of specific porphyrins, as described in the literature,[9] carried out. In all three instances, excessive quantities of porphyrins were demonstrated by ether extraction, but this fraction was certainly only a small part of the total colorless porphyrins present. In cases 1 and 3 the identification of the ether extract as a porphyrin mixture was not only shown by fluorescence in ultraviolet light but also confirmed by spectroscopic examination. In cases 1 and 2 the urine was often deep orange to red in color with increased intensity on exposure to light and when colored consistently gave a positive reaction to the aldehyde test with production of a chloroform-insoluble pigment, presumably porphyobilinogen.[5] The third patient had urine of normal color with large amounts of colorless porphyrins, but it did not contain the reddish brown porphobilin or its precursor porphobilinogen or other pigments commonly found in acute porphyria.[10] In no case was the porphyrin content of the feces determined.

According to the classification set forth by Mason and his co-workers [1b] all these cases fall into the category of acute porphyria, but whether there is sufficient evidence to implicate a single toxic factor in any of the cases is open to question. There was no definite family history of symptoms of porphyria in any of the 3 cases, whereas in cases 1 and 2 there were family histories of diabetes.

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7. Berg, M.: Acute Porphyria: Clinical and Pathologic Observations, Arch. Int. Med. **76**:335-340 (Nov.-Dec.) 1945.

8. Prunty, F. T. G.: Acute Porphyria, Arch. Int. Med. **77**:623-642 (June) 1946.

9. Dobriner and Rhoads.[1a] Watson.[1f] Prunty.[8]

10. Nesbitt and Watkins.[1c] Goodman and Gilman.[5]

The cases here reported are too few to support a hypothesis that diabetes mellitus and porphyria are causally related. Further light may be shed on this question by the performance of glucose tolerance tests in patients with porphyria and by urinary porphyrin studies in patients with diabetes, especially those thought to have "diabetic polyneuritis."

In the early stages the differentiation of porphyria and diabetic neuritis may be difficult inasmuch as both may involve aching pains in the limbs, muscular tenderness, hyperesthesia and various types of paresthesia, weakness, muscular atrophy, diminution or absence of tendon reflexes and loss of various sensory modalities, including vibration sense, demonstrable by objective tests.[11] The arms, the legs or the trunk may be most affected in porphyria, whereas diabetic polyneuritis usually involves primarily the lower extremities. In some cases of porphyria the proximal (girdle) musculature of the hips and shoulders is predominantly affected, as may be the case in the Guillain-Barré syndrome but not ordinarily in other neuritides. The diagnosis of porphyria is favored by the occurrence of severe abdominal pains simulating those of an acute surgical condition of the abdomen, with radiation to the lumbar, sacral or femoral regions, and by the dramatic and bizarre manifestations of excitement, delirium, hallucinations and convulsions. Inspection of the urine and examination for porphobilinogen and porphyrins may elucidate some otherwise baffling diagnostic problems.

SUMMARY

Three cases with concomitance of diabetes mellitus and porphyria among a total of 8 cases of porphyria recorded at the Albert Merritt Billings Hospital are described. In each instance, diabetes preceded the onset of symptoms of porphyria.

It is suggested that glucose tolerance tests be performed in cases of porphyria and that urinary porphyrins be sought in cases of diabetes, especially those in which the condition is thought to be "diabetic polyneuritis."

11. Brain, W. R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940.

MULTIPLE MYELOMA WITH NEW BONE FORMATION

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THERE is unanimity of opinion among authorities on the subject that the typical and characteristic lesion of bone in multiple myeloma is a discrete osteolytic involvement. The roentgenographic appearance is usually that of a punched-out area with sharp margination and without evidence of surrounding productive reaction. In a description of multiple myeloma Boyd [1] stated, "It is a pure rarefying lesion with no formation of new bone." To quote Geschichter [2]: "The widespread occurrence of small, sharply demarcated defects in the marrow cavity, unaccompanied by bending deformity or the formation of new bone, are the cardinal features in the diagnosis of multiple myeloma." Snapper [3] affirmed that in multiple myeloma "no new formation of bone takes place." Shanks, Kerley and Twining [4] declared categorically concerning the osseous lesions of multiple myeloma that "they are entirely osteolytic, and never give rise to new bone formation."

The case to be presented is of unusual interest because it has been possible to demonstrate conclusively by histologic and roentgenographic study the formation of new bone in a patient with proved multiple myeloma. A search of the literature of this disease has brought to light no other case in which a significant degree of new bone formation, aside from that occurring at the site of pathologic fracture, was visualized on histologic and roentgenographic examination.

From the Medical Service, Dr. S. Biloon, Director, Dr. William Aronson, Pathologist, and Dr. Samuel Weitzner, Radiologist, Morrisania City Hospital.

1. Boyd, W.: A Text-Book of Pathology: An Introduction to Medicine, Philadelphia, Lea & Febiger, 1934, p. 968.

2. Geschichter, C., in Pillmore, G.: Clinical Radiology: A Correlation of Clinical and Roentgenological Findings, Philadelphia, F. A. Davis Company, 1946, vol. 2, p. 614.

3. Snapper, I.: Medical Clinics on Bone Diseases: A Text and Atlas, New York, Interscience Publishers, Inc., 1943, p. 36.

4. Shanks, S. C.; Kerley, P., and Twining, E. W.: A Text-Book of X-Ray Diagnosis, London, H. K. Lewis & Co., Ltd., 1939, vol. 3, p. 630.

REPORT OF A CASE

History.—P. K., a 68 year old white woman, was admitted to Morrisania City Hospital on Jan. 3, 1949 for the first time. She had been well until six months prior to entry, when she had begun to complain of mild but steady headache. About four months later her right eye began to swell, and insidious weakness of the left arm, and subsequently of the left leg, was noted. She complained of double vision. She was then taken to an oculist, who, in turn, referred her to a neurologist. The latter made a diagnosis of cerebral thrombosis. The patient continued up and about until ten days before admission, at which time she became totally bedridden. Anorexia had developed, and she had lapsed into semistupor. There was no definite weight loss, no melena and no vaginal discharge or bleeding. The patient, however, had vomited occasionally since the onset of her illness. Concomitant with the

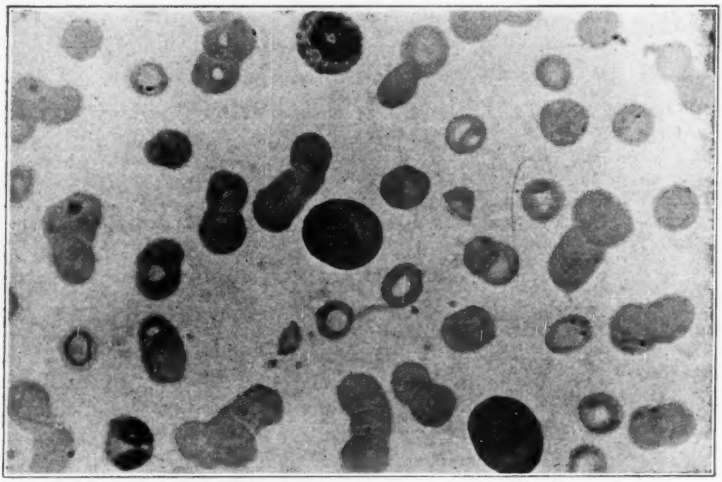

Fig. 1.—Smear of peripheral blood showing plasma cells. At one examination 70 per cent of the leukocytes were comprised of these cells.

ocular disturbances appeared several soft swellings on her forehead, not associated with any trauma.

Examination.—The patient was an elderly white woman lying quietly in bed, semicomatose but able to be aroused by painful stimuli, unable to speak and apparently unable to understand speech. Her blood pressure was 120 systolic and 60 diastolic, her pulse rate 80 per minute and her temperature 98.6 F. On her forehead were several soft, resilient, cystic, walnut-sized swellings. On palpation these were found to overlie actual circular defects in the frontal bone. Examination of the eyes disclosed the right eye to be proptosed and immobile. The pupil was dilated and did not react to light. The left eye was normal. Both fundi revealed blurred disks. Examination of the heart, lungs and abdomen revealed no abnormalities. There was no adenopathy, no splenomegaly and no hepatomegaly. Neurologic examination disclosed a definite hemiparesis on the left. The patient was seen by the neurologic consultant, whose opinion it was that she had a lesion of the mid-

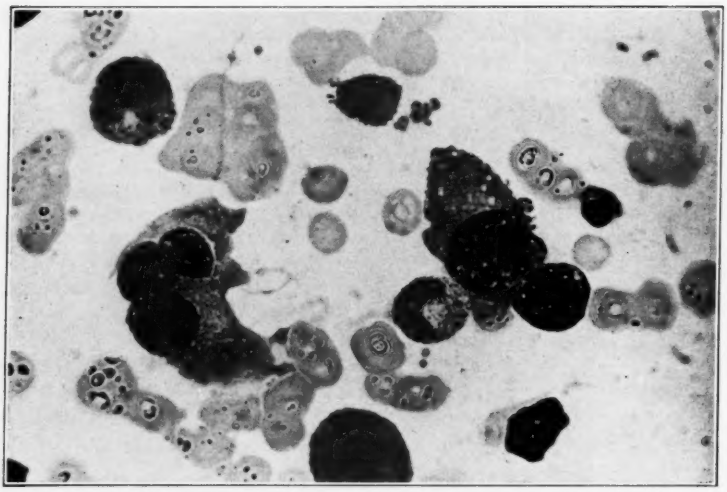

Fig. 2.—Smear of sternal marrow. The bone marrow is characteristic of extremely malignant multiple myeloma.

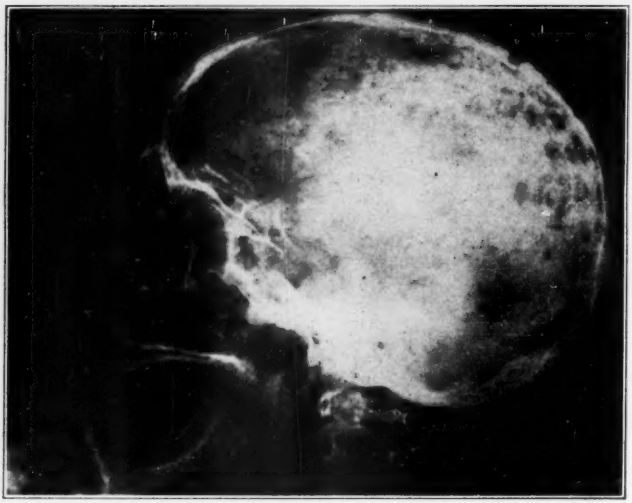

Fig. 3.—Extensive area of destruction in the frontal bone. There is a great number of small punched-out areas.

brain due to metastatic brain disease. A spinal tap was performed. The initial pressure was 150 mm. of water. All cytologic, chemical and serologic observations were within normal limits.

Laboratory Data.—Routine urinalysis revealed no abnormalities. The total protein content of the blood was 7.8 Gm. per hundred cubic centimeters (albumin 4.2 Gm. and globulin 3.6 Gm.). The albumin-globulin ratio was 1.2:1. The serum cholesterol level was 326 mg. per hundred cubic centimeters; cholesterol esters, 97 mg.; acid phosphatase, 2.3 Gutman units; alkaline phosphatase, 10.4 King-

Fig. 4.—Diffuse productive process involving the entire shaft of the left humerus. Dense bony spicules are arranged at right angles to the shaft proper. A pathologic fracture is evident. The proximal portion of the left radius was similarly involved.

Armstrong units; serum calcium, 15.0 mg., and phosphorus, 2.8 mg. The cephalin flocculation reaction was 4 plus in twenty-four hours. Calcium excretion in both urine and stool was increased. The urine showed the presence of Bence-Jones protein on several occasions. A blood count revealed 3,400,000 erythrocytes and 8,000 leukocytes, of which 24 per cent were polymorphonuclear, 4 per cent transitional and 70 per cent plasma cells with dense eccentric nuclei containing chromatin in spokelike fashion and bluish gray cytoplasm (fig. 1). Repeat blood counts were

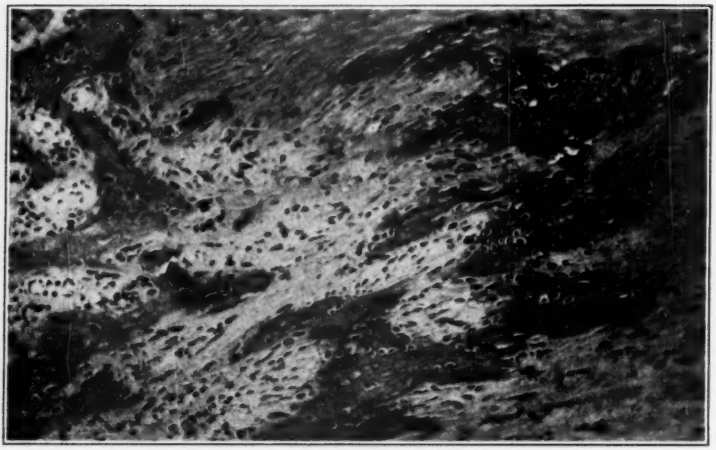

Fig. 5.—Osteoid and scar tissue with diffuse infiltration by myeloma cells in the vicinity of the fracture. Hematoxylin and eosin stain; × 100.

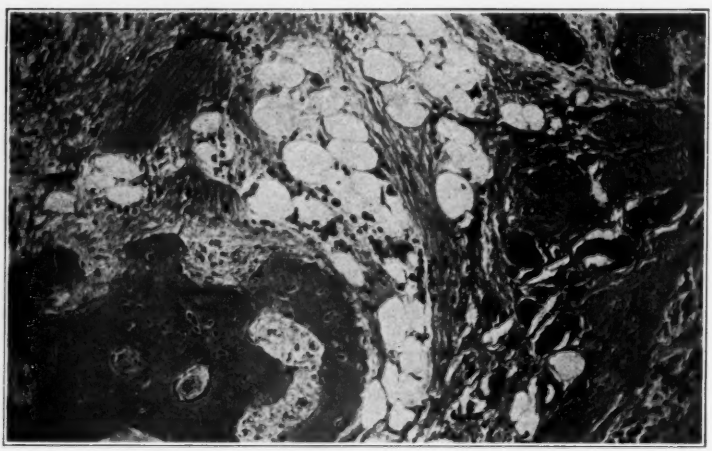

Fig. 6.—Section of periosseous tissues, showing newly formed trabeculae in the lower left and upper right corners, adipose tissue, fibrous tissue and voluntary muscle fibers. There is diffuse infiltration by myeloma cells. Hematoxylin and eosin stain; × 100.

done. The total white cell count ranged from 9,000 to 35,000, and plasma cells comprised between 40 and 70 per cent of the total on various occasions. Aspiration of sternal marrow revealed that the marrow was almost entirely replaced by plasma cells (fig. 2).

One of the nodules on the patient's forehead was removed and on histologic study was found to consist of islets of plasma cells in a fibrous stroma.

Roentgenographic examination of the pelvis showed no abnormalities. Studies of the skull (fig. 3) revealed a great number of small punched-out areas of less density than the surrounding bone. There was an extensive area of destruction in the frontal bone. The femurs, clavicles and right humerus disclosed numerous small cystic punched-out areas. The left humerus (fig. 4) showed a diffuse productive process involving the entire shaft and producing a shaggy appearance. Dense bony spicules were arranged at right angles to the shaft proper along most of the bone. There was a pathologic fracture at the lower end of the humerus. The proximal portion of the left radius revealed a pathologic fracture and productive bone changes similar to those seen in the humerus.

Biopsy of the left humerus was performed. A series of sections prepared from random fragments removed from the vicinity of the fracture and several other points along the shaft disclosed unequivocal evidence of extensive new bone formation in association with myeloma (fig. 5). Several areas of soft tissues were diffusely infiltrated by myeloma and here, too, there appeared to be a tendency toward laying down of osteoid and osseous tissue (fig. 6). Review of many sections led to the impression that most of the new bone formation arose from the periosteum. The marrow, wherever present, was extensively transformed into myeloma. Several fragments presented an intermixture of areas of osteoid tissue, fibrosis and necrobiosis of the original cortex which suggested the usual tissue reactions to fracture. The general impression was that a unique response on the part of the periosteum to irritation by infiltrating tumor resulted in the formation of the extraordinary deposits of bony tissue disclosed by the roentgenograms.

Course.—A week after admission the patient was found to have a painless pathologic fracture of the lower end of the left humerus. She remained semistuporous throughout her stay in the hospital. She was fed by clysis and infusion and was given several transfusions. Stilbamidine® (4-4′-diamidinostilbene) therapy was started shortly before her death, which occurred three weeks after entry. Autopsy was not done.

COMMENT

We have read many protocols of autopsies in which multiple myeloma was seen without finding reference to new bone formation other than that occurring at the site of pathologic fracture and resulting in union of the fragments, a mechanism clearly unrelated to the disease process itself. Harbitz [5] and also Schmorl [6] have described what they termed "thickening" occurring in the skull and in the tubular bones some distance from the area of bone absorption. Close scrutiny of their material discloses no parallelism whatever to the case herein reported;

5. Harbitz, F.: Multiple primære svulster i bensystemet (myelosarkoma), Norsk. Mag. f. Lægevidensk. **1**:89 and 169 (Jan.-Feb.) 1903.

6. Schmorl: Fall von Myelom, München. med. Wchnschr. **59**:2891 (Dec. 24) 1912.

unequivocal evidence of new bone formation was not cited or adduced; there were no roentgenograms. Geschickter and Copeland [7] in 1928, in a review of all the cases of proved multiple myeloma appearing in the literature up to that time, stated, "The tumors themselves are bone destructive and frequently show up in the pictures as rounded, punched-out areas varying from the size of a pea to that of an orange. Sometimes they are more diffuse, giving a rarefied osteoporitic appearance to the roentgenogram, or, when multiple areas have become confluent, resembling mottling." In a recent report of 61 cases of multiple myeloma by Adams, Alling and Lawrence [8] the roentgen findings are summarized as being those of, first, osteoporosis; second, small "flea-bitten" areas of rarefaction without evidence of new bone formation; third, and most characteristic, the "punched-out" area with its sharp margination without evidence of surrounding osteoblastic change, and, fourth, in a few cases, no roentgen changes of any type. Our case, therefore, appears to be unique in that new bone formation in multiple myeloma occurred in marked degree, as was conclusively shown by histologic and roentgenographic examination.

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Dr. Joseph C. Ehrlich gave valuable assistance in preparing the manuscript.

7. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, Arch. Surg. **16**:807 (April) 1928.

8. Adams, W. S.; Alling, E. L., and Lawrence, J. S.: Multiple Myeloma: Its Clinical and Laboratory Diagnosis with Emphasis on Electrophoretic Abnormalities, Am. J. Med. **6**:141 (Feb.) 1949.

PERIARTERITIS NODOSA

Study of Chronicity and Recovery, with Report of Two Cases

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DETROIT

THE PURPOSE of this communication is to reevaluate the prognosis in periarteritis nodosa in the light of the reports in the literature and the personal experiences noted herein. In the past, the course of the disease has been regarded as leading to a fatal termination. This, undoubtedly, is the outcome in the majority of instances. There have been cases, however, in which the disease has taken a chronic course, others with long, complete remissions and a few in which recovery has been reported. Two cases in which recovery occurred are presented.

In 1852, von Rokitansky [1] first described the pathologic changes of the disease entity periarteritis nodosa. It remained for Kussmaul, however, to recognize it as a clinical syndrome. With Maier,[2] in 1866, he reported 2 cases of a "hitherto undescribed peculiar disease of the arteries which is accompanied by Bright's disease and is a rapidly progressive, general paralysis of the muscles." The disease as described was chronic, diffuse, obscure in origin and of serious prognosis.

There have been many excellent reviews of periarteritis nodosa, the best among them being those by Lamb,[3] Ophüls,[4] Gruber,[5] Singer,[6]

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1. von Rokitansky, C.: Ueber einige der wichtigsten Krankheiten der Arterien, Denkschr. d. k. Akad. d. Wissensch. **4**:1, 1852.

2. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, Deutsches Arch. f. klin. Med. **1**:484, 1866.

3. Lamb, A. R.: Periarteritis Nodosa: A Clinical and Pathological Review of the Disease, Arch. Int. Med. **14**:481 (Oct.) 1914.

4. Ophüls, W.: Periarteritis Acuta Nodosa, Arch. Int. Med. **32**:870 (Dec.) 1923.

5. Gruber, G. B.: Zur Frage der Periarteritis nodosa, mit besonderer Berücksichtigung der Gallenblasen- und Nieren-Beteiligung, Virchows Arch. f. path. Anat. **258**:441, 1925.

6. Singer, H. A.: Periarteritis Nodosa, with Special Reference to the Acute Abdominal Manifestations: Report of Two Cases, Arch. Int. Med. **39**:865 (June) 1927.

Strong,[7] Curtis and Coffey,[8] Middleton and McCarter,[9] Spiegel,[10] Harris, Lynch and O'Hare,[11] Grant [12] and Miller and Daley.[13]

Klotz,[14] early in 1917, stated that the mortality rate was 100 per cent. He recognized however, that that situation might prevail because a proper diagnosis was being reported only in the fatal cases at that time. Two reasons were advanced for this lack of clinical recognition: "As the typical lesions are found upon the vessels of internal organs, the skin being involved in only a few cases, no opportunity is given the clinician to analyze the lesions. Undoubtedly in many instances a similar localization and infection of milder character involves various systems of the arteries, but in the absence of marked clinical signs or serious pathological change, the cases proceed to recovery without our attention being called to the characteristic lesion." Thus it was early suggested that because of difficulty in diagnosis and because mild forms of the condition might go unrecognized, periarteritis nodosa might exist in other than an acutely fatal form.

Many writers have stressed the high fatality rate but have also mentioned cases in which there were chronic courses, remissions and apparent recoveries. Haining and Kimball [15] stated the view that periarteritis nodosa is a progressive and incurable disease. That belief they supported with the data on rapidly fatal termination in most reported cases, in nearly all of which there was histologic evidence of acute inflammation as well as chronic reparative changes. However, they agreed that "in spite of the dubious prognosis, there can be no doubt that occasionally the process comes to a halt." Leishman,[16] writing in 1937, stated: "The disease seems almost invariably fatal although four undoubted cases have recovered and its seems likely that an occasional

7. Strong, G. F.: Periarteritis Nodosa, Canad. M. A. J. **19**:534 (Nov.) 1928.

8. Curtis, A. C., and Coffey, R. M.: Periarteritis Nodosa: A Brief Review of the Literature and a Report of One Case, Ann. Int. Med. **7**:1345 (May) 1934.

9. Middleton, W. S., and McCarter, J. C.: Diagnosis of Periarteritis Nodosa, Am. J. M. Sc. **190**:308 (Sept.) 1935.

10. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993 (Dec.) 1936.

11. Harris, A. W.; Lynch, G. W., and O'Hare, J. P.: Periarteritis Nodosa, Arch. Int. Med. **63**:1163 (June) 1939.

12. Grant, R. T.; Observations on Periarteritis Nodosa, Clin. Sc. **4**:245 (Oct.) 1940.

13. Miller, H. G., and Daley, R.: Clinical Aspects of Polyarteritis Nodosa, Quart. J. Med. **15**:255 (Oct.) 1946.

14. Klotz, O.: Periarteritis Nodosa, J. M. Research **37**:1 (Sept.) 1917.

15. Haining, R. B., and Kimball, T. S.: Periarteritis Nodosa, Am. J. Path. **10**:349 (May) 1934.

16. Leishman, A. W. D.: The Clinical Diagnosis of Polyarteritis Nodosa, Lancet **1**:803 (April 3) 1937.

case may recover unrecognized." Sandler,[17] too, stressed the high fatality rate, stating that when the disease is confined to structures less vital than the heart and kidneys a complete cure is possible once the lesions have healed. Although the patient may survive the acute stage, he wrote, when the vital organs are involved he will eventually die of cardiac or renal failure due to the healed lesions of the arteritis. Similarly, Lummis[18] mentioned the almost invariably fatal outcome. He stated the belief that the favorable outcomes were due to remissions: "It is not unlikely that there exists a form milder than the usual fatal one but it is at present below the diagnostic level." Baker,[19] in a review in 1942, noted that the disease was fatal in the majority of cases. However, he estimated that 10 per cent of patients recovered.

Periarteritis nodosa is not invariably fatal. In the past, interest in the disease was primarily on the part of the pathologist, so that only the cases coming to necropsy were reported. However, by 1940, Grant[12] could state that of 350 reported cases the diagnosis was established ante mortem in 50. Many more cases can be added to this list as of the time of writing. Further clinical recognition will result from an elevated "index of suspicion" and the more frequent use of biopsy. Weiss[20] wrote that the prognosis of the disease would improve when it was recognized oftener clinically. Remissions, long intermissions and exacerbations he recognized as being common in the natural history of periarteritis nodosa.

Two cases are presented as additional instances of recovery from periarteritis nodosa.

REPORT OF CASES

CASE 1.—J. McC., a white man of 21, has been asymptomatic for the past year at the time of this report, having recovered from two episodes of periarteritis nodosa at the ages of 7 and 20; he remained entirely well for the interval of twelve years.

First Admission (table 1.)—The patient was admitted to the Boston City Hospital for the first time in January 1935 at the age of 7. A history of a normal birth was obtained; measles and whooping cough were the only previous illnesses.

The family history was significant only in that the mother had hay fever and asthma, being sensitive to the pollen of ragweed and goldenrod.

One week prior to admission, the child complained of a sore throat. This was followed by soreness and stiffness of the legs, feverishness, restlessness and

17. Sandler, B. P.: Periarteritis Nodosa: Report of Case Diagnosed Clinically and Confirmed by Necropsy, Am. J. M. Sc. **195**:651 (May) 1938.

18. Lummis, F. R.: Periarteritis Nodosa, Ann. Int. Med. **10**:105 (July) 1936.

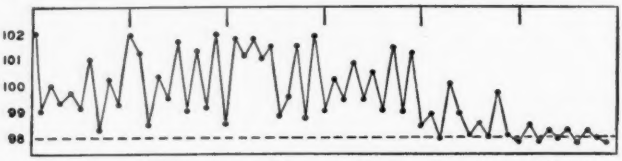
19. Baker, L. A.: Periarteritis Nodosa, with Report of Two Cases, Ann. Int. Med. **17**:223 (Aug.) 1942.

20. Weiss, S.: Arteritis: Diseases Associated with Inflammatory Lesions of the Peripheral Arteries, New England J. Med. **225**:579 (Oct. 9) 1941.

anorexia. The child was confined to bed with increasing pain in the right knee; the left knee then became painful and tender. On the day of hospitalization, abdominal pain appeared.

Physical Examination: The child was well developed but poorly nourished and acutely ill. The left wrist, the right ankle and both knees were swollen, warm, tender and painful on motion. The tonsils were hypertrophic and hyperemic. The heart was normal in size. At the apex was a soft systolic murmur,

TABLE 1.—*Course of the Disease in Case 1 at the Time of the First Hospitalization, When the Patient Was 7*

	Duration, Months					
	1	2	3	4	5	6 and 7
Temperature, F.						
Cutaneous lesions	0	Hemorrhagic purpura; subcutaneous nodules; gangrene of finger tips	Erythematous maculopapules	Lesions subsiding; biopsy revealed periarteritis nodosa	Necrotic finger tips sloughed	Transitory nodules (1 wk.) amputated finger tips
Painful, swollen joints *	++++	++++	+++	++	+	0
Lymphadenopathy	0	0	0	0	0	0
Blood count						
Total white blood cells	22,600-39,000	64,000	36,000-55,000	47,000	20,050	13,800
Polymorphonuclear leukocytes, %	80	88	70	88	74	68
Eosinophils, %	2	0	4	0	9	4
Hemoglobin, Gm.	10.5	7.5	7	7.5	8.8	10
Red blood cells	4.71	4.65	4.50	4.8	4.9	4
Urinalysis	Occasional white and red blood cells	Occasional red blood cells	Rare red blood cells	0	0	0
Drugs	Sodium salicylate	Sodium salicylate	Sodium salicylate	0	0	0

* Basis of 0 to ++++.

transmitted upward to the base. The blood pressure was 100 systolic and 64 diastolic.

Laboratory Studies: The hemoglobin concentration was 10.6 Gm. per cubic centimeter of blood (71 per cent); there were 4,700,000 erythrocytes and 22,600 leukocytes per cubic millimeter; the differential smear contained 80 per cent neutrophils, 14 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils.

Course: During the first month of hospitalization, the condition of the joints remained unchanged. Sodium salicylate was administered orally, and methyl salicylate was applied locally. Tachycardia with a rate of 110 to 120 persisted. The total white cell count rose steadily to 39,200. No albuminuria or glycosuria was noted. Blood cultures were sterile.

In the second month, lesions of hemorrhagic purpura appeared on the extremities and back. The finger tips became painful and discolored, and dry gangrene followed. Subcutaneous nodules appeared scattered over the body with some located in relation to the blood vessels.

During the third month, the symptoms in the joints began to subside, and the hemorrhagic purpura subcutaneous nodules began to resolve. Erythematous maculopapular lesions appeared on the chest. The gangrenous finger tips continued to separate. Tachycardia with a rate of 100 to 120 persisted. On roentgenograms the chest and joints appeared normal. The electrocardiogram revealed sinoatrial tachycardia, a P-R interval of 0.12 second and right axis deviation.

The fourth month of hospitalization was characterized by the persistence of the fever and tachycardia. Biopsy of a subcutaneous nodule from the abdomen was done (fig. 1). Pain was present in both hands, and the necrotic terminal phalanges continued to separate.

During the fifth month, the pulse rate varied from 80 to 120. The necrotic finger tips sloughed, and healing supervened. The joints were only slightly tender. The differential smear contained 74 per cent neutrophils, 13 per cent lymphocytes, 9 per cent eosinophils and 4 per cent monocytes. The electrocardiogram revealed sinoatrial tachycardia with a P-R interval of 0.12 second.

During the last two months of hospitalization (the sixth and seventh), the pulse was normal. At the end of the sixth month, a new crop of skin lesions appeared. These were subcutaneous nodules measuring 1 to 2 cm. in diameter and covered by erythematous skin. The amputated phalanges healed.

The patient's general condition improved. He remained ambulatory and active about the ward. His appetite was good, and a marked gain in weight occurred. The leukocyte count fell to 13,800. The differential smear contained 68 per cent neutrophils, 26 per cent lymphocytes, 4 per cent eosinophils and 2 per cent monocytes. The examination of the urine was entirely noncontributory.

Interval.—The patient was discharged in the care of his mother. He enjoyed good health in the following twelve years, and his physical development was normal. In recent years, he worked at chrome plating, which necessitated the use of nitric, sulfuric and chromic acids; as a result, burns of the hands were not uncommon.

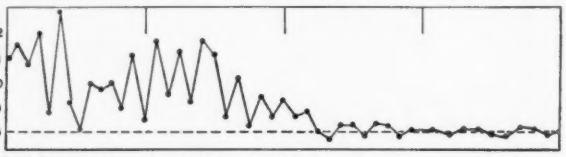
Second Admission (table 2.)—Pain and weakness of both forearms appeared in April 1947. The patient's family physician made a tentative diagnosis of rheumatic fever and instituted penicillin therapy. With the increasing severity of symptoms and the onset of severe toothache, the patient was admitted to the hospital two weeks later.

The symtomatic tooth was extracted. The report was "pulpitis, right third molar, without dental cause." The tooth did not show carious lesions clinically or roentgenographically, the changes being consistent with ischemia.

Physical Examination: On admission to the medical ward, the patient appeared acutely ill and in considerable pain. The lower extremities were abducted at the hips and flexed at the knees. The upper extremities were flexed on the chest. Slight movement was resisted because of pain. The oral temperature was 101 F., the pulse rate 100 and the respiration rate 25. The blood pressure was 160 systolic and 85 diastolic. The skin was warm and dry. On both calves were circumscribed, indurated, nontender nodules, which were 1 cm. in diameter and pink. Reddish violet maculopapular lesions, 1 to 2 cm. in diameter and discrete and nontender, some of which showed typical iris configuration, were present on the medial aspect of the right foot. On the volar surface of each forearm was an erythematous

blush. Pronounced generalized tenderness of the muscles was present, especially prominent in the paravertebral muscles of the back, the sternocleidomastoid muscles and those of the anterior abdominal wall and the extremities. There was swelling of the muscle groups of the extremities and increased firmness, to a rubbery consistency. Cervical resistance to flexion was noted. Many teeth were carious. Moderate enlargement and tenderness of the cervical, axillary and inguinal lymph nodes were present. The lungs were clear, and there were no cardiac

TABLE 2.—*Course of the Disease in Case 1 at the Time of the Second Hospitalization, When the Patient Was 20*

	Duration, Months			
	1	2	3	4
Temperature, F				
Cutaneous lesions	Nodules, maculopapules, erythema; biopsy revealed acute periarteritis nodosa	Increased numbers of nodules and macules appeared and faded; gangrene formed and sloughed	Lesions subsiding; biopsy revealed healing periarteritis nodosa	0
Painful, swollen muscles and joints *	++++	+++ to +	+ to 0	0
Lymphadenopathy *	++	++	0	0
Blood count				
Total white blood cells	26,300	12,000-16,000	7,450	8,750
Polymorphonuclear leukocytes, %	89	66	66	67
Eosinophils, %	0	3	6	6
Hemoglobin, Gm.	14	9	12.5	12.5
Red blood cells	4.6	4	4.5	4.5
Urinalysis	0	0	0	0
Drugs	Penicillin; sodium salicylate 1st & 2nd wk.; tripelennamine hydrochloride 3rd & 4th wk.; meperidine hydrochloride ("demerol hydrochloride")	Tripelennamine hydrochloride; meperidine hydrochloride; codeine	0	0

* Basis of 0 to ++++.

murmurs. The ophthalmoscopic examination was noncontributory. The pulse was easily palpable in the radial, the posterior tibial and the dorsalis pedis arteries.

Laboratory Examination: The leukocyte count was 26,300. The differential smear contained 14 per cent juvenile and 75 per cent mature neutrophils and 11 per cent lymphocytes. The corrected sedimentation rate (Wintrobe method) was 30 mm. per hour, the hemoglobin concentration 14 Gm. (95 per cent), the hematocrit reading 40 and the icterus index 5. Other blood chemistry values were nonprotein nitrogen 34 mg., total protein 5.6 Gm. (albumin 2 Gm., globulin 3.6 Gm.) and cholesterol 219 mg. per hundred cubic centimeters. The blood cultures

were sterile. Cultures of material from the throat were positive for alpha hemolytic streptococci, diphtheroids and Neisseria catarrhalis. Biopsy of a subcutaneous nodule was done (fig. 2).

Course: The course for the next month was stormy. The temperature remained elevated, reaching peaks of 102 to 103 F. (oral). The pulse rate showed a proportional rise. The weakness was progressive; the patient had to be turned in bed. Irritability, generalized pain and tenderness made nursing care difficult. Anorexia was pronounced and the loss of weight was progressive.

At the conclusion of the first week of hospitalization, there occurred three consecutive seizures. These were characterized by a loss of consciousness and by generalized convulsive movements of three to five minutes' duration; the interval between seizures was approximately five minutes, and stupor followed them. The tendon reflexes were noted to be hypoactive on the right side, and bilateral extensor plantar reflexes were obtained. Examination of the spinal fluid revealed an initial pressure of 195 mm. of water, 3 lymphocytes per cubic millimeter and a total protein value of 15 mg. per hundred cubic centimeters. The responses to the Pandy and colloidal gold tests were negative. On the following day, there was evidence of muscular weakness in the lower right side of the face. The tendon reflexes were equal on the two sides, and the plantar responses were flexor. The sensory modalities were normal.

The cutaneous lesions on the medial aspect of the right foot and the flexor surface of both forearms became ecchymotic. The lesions on the right foot became confluent, with a well defined border. On the calves and the flexor surfaces of the arms, pea-sized nodules appeared, which were pink and only slightly tender; these did not appear to follow any anatomic structure. Toward the end of the first month, violaceous macules were noted on the pectoral girdle. The pigmented lesions on the volar surface of the left forearm began to fade, whereas those on the right turned brown and began to slough.

The generalized tenderness of the muscles diminished slowly. Induration and swelling remained in the forearms and the muscles of the calves. In these muscle groups, the tenderness was most marked. Flexion contractures developed in the fingers, wrists, elbows and knee joints. Passive movement produced pain.

The initial medication was as indicated in table 2. Administration of the antihistamine agent tripelennamine hydrochloride (pyribenzamine hydrochloride®) was begun, a daily dose of 350 mg. being given.

During the second month of hospitalization, there was improvement in the patient's strength and appetite. Less pain was experienced, but liberal amounts of acetylsalicylic acid and codeine were still necessary. The necrotic epidermis on the volar surface of the right forearm sloughed, leaving a pink, granulating area. On the medial aspect of the right foot, the cutaneous lesions continued to fade and the epidermis desquamated. Toward the end of the second month, a new crop of nodules similar to those previously described appeared on the arms and calves. There was no associated systemic exacerbation.

With the application of splints and with physical therapy, the flexion deformities improved and some degree of motion returned at the joints.

The urine was consistently normal. The hematocrit reading was 31 and the erythrocyte count 4,000,000. The differential count showed 6 per cent juvenile and 60 per cent mature neutrophils, 28 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 25 mm. per hour. The total protein value was 7.45 Gm. (albumin 3.64 Gm., globulin 3.81 Gm.). The blood cultures remained sterile.

At the end of the second month of hospitalization, analgesics were still necessary for the control of pain.

In the third month, rapid improvement took place. With a better appetite, the patient showed a gain in weight. The pain disappeared entirely. The pulse returned to normal. All rigidity of the muscles disappeared. A full range of motion returned to all joints, and the patient became ambulatory. The hematocrit reading rose to 33. The differential count showed 66 per cent neutrophils, 26 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils. The value for nonprotein nitrogen was 29 mg. per hundred cubic centimeters. The sulfobromophthalein test for liver function (5 mg. was given per kilogram of body weight) showed 4 per cent dye retention in forty-five minutes. The phenolsulfonphthalein test (intravenous injection) revealed that 40 per cent of the dye was excreted in fifteen minutes and 85 per cent in two hours. A biopsy of a resolving subcutaneous nodule was made (fig. 3).

The fourth and final month of hospitalization was one of convalescence. The patient was fully ambulatory and aided in the ward work. A full range of motion returned to all the extremities. The appetite was good, and a gain in weight was recorded. The hands remained mottled and were constantly cool and moist. The heart and lungs were not remarkable. Results of the neurologic examination were noncontributory, the facial weakness having disappeared.

During the entire illness, there was no evidence of pulmonary, cardiac or renal involvement. Roentgenograms of the chest showed the lung fields to be clear and the cardiac size and configuration to be normal. Repeated electrocardiographic tracings were normal (the P-R interval was 0.13 to 0.16 second, the Q-S interval 0.09 second and the T waves upright in all leads; there was right axis deviation). The blood pressure, which originally showed a slight systolic elevation (160 systolic and 85 diastolic), was normal on the discharge of the patient (130 systolic and 80 diastolic).

Condition After Discharge.—One year after discharge from the hospital, the patient was entirely well and at work driving a delivery truck. On exposure to cold, he stated, his hands became a mottled blue color and were uncomfortable. This disappeared readily on warming. Physical and laboratory examinations were entirely noncontributory. The pulse rate was 80 and the blood pressure 124 systolic and 74 diastolic. The urine was normal. Examination of the blood revealed 14 Gm. of hemoglobin (95 per cent) with a hematocrit reading of 42. The leukocyte count was 7,100 and the differential count normal.

Microscopic Examination.—The first biopsy (fig. 1), done in April 1935, showed a small artery, the lumen of which was of pinpoint size owing to endothelial proliferation. There was infiltration of all coats and of the surrounding fat by lymphocytes, neutrophils and eosinophils. Fibroblastic proliferation was present in the adventitia and muscularis. Other sections showed the acute inflammatory reaction involving medium-sized subcutaneous arteries. One such vessel had the lumen occluded by a partially organized thrombus and large numbers of neutrophils. A heavy infiltration of neutrophils involved all coats, from the intima to the adventitia.

The second biopsy (fig. 2) made twelve years later during the acute phase of the second admission, showed an acute, necrotizing, inflammatory process involving a small artery of skeletal muscle. Fibrinoid necrosis of the media and subintima was pronounced, with infiltration of neutrophils in all the coats and the surrounding tissue.

Fig. 1.—Photomicrograph of subcutaneous nodule made during the fourth month of the first admission in case 1, showing a small artery with endothelial proliferation and cellular infiltration. × 200.

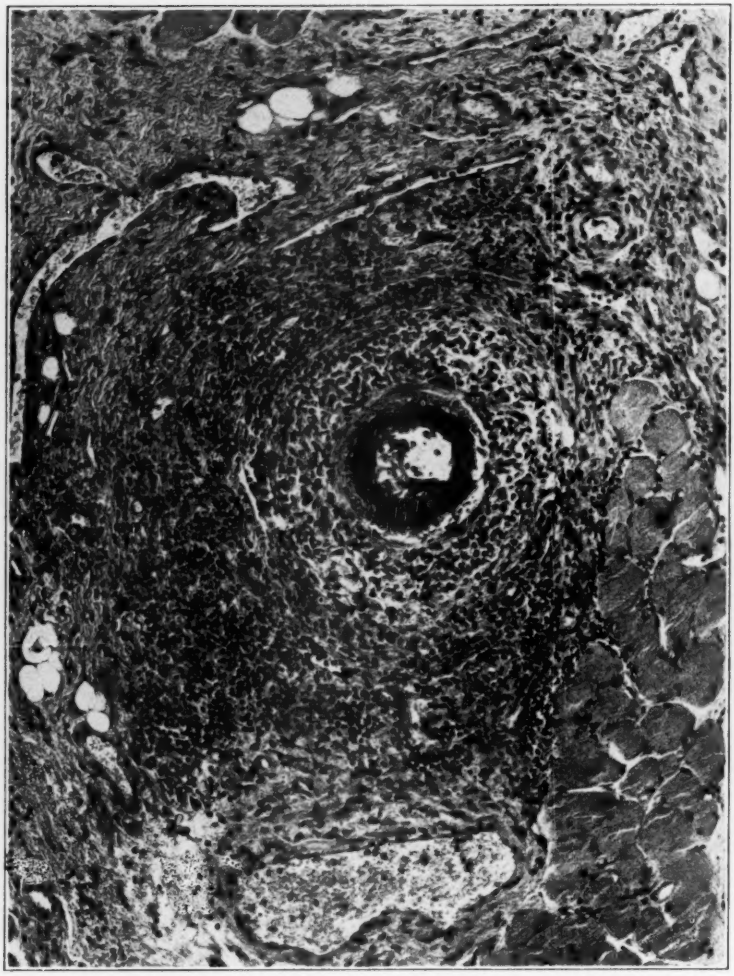


Fig. 2.—Photomicrograph of section of muscle made during the acute stage of the second admission in case 1, showing acute necrotizing periarteritis. × 200.

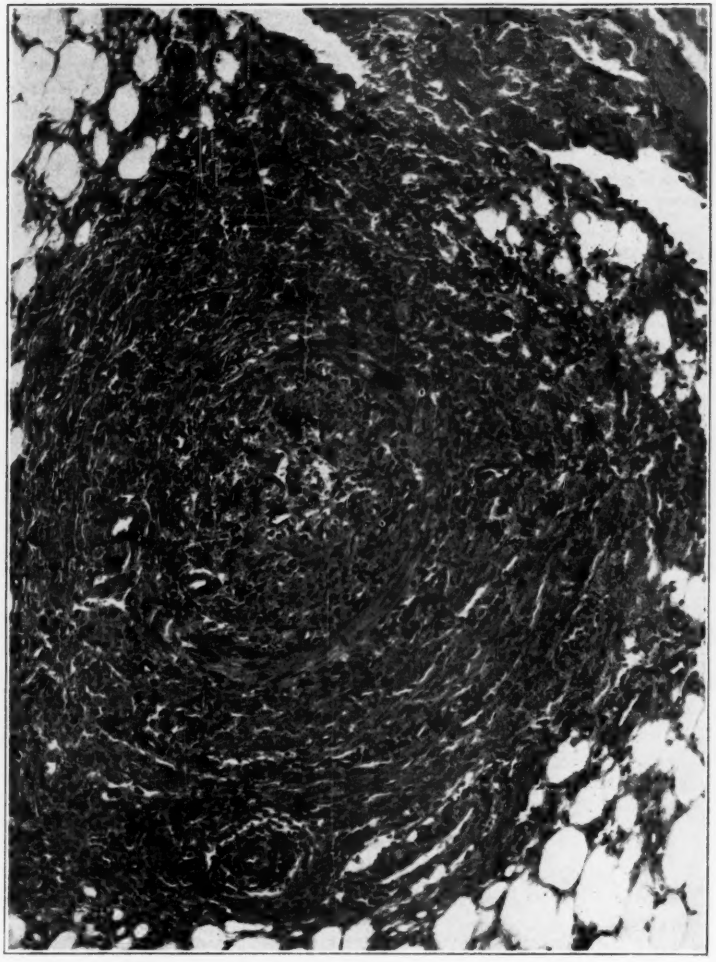


Fig. 3.—Photomicrograph of section of skin obtained during the healing stage of the second admission in case 1, showing a small artery with a thrombosed lumen, subacute inflammatory infiltration and fibrosis. × 200.

The third biopsy (fig. 3), made during the healing phase of the second admission, showed a small subcutaneous artery with the lumen occluded by cellular fibrous tissue. Several small, irregular, endothelium-lined spaces, some containing erythrocytes, were present within the thrombus. The intima and portions of the muscularis were replaced by cellular fibrous tissue. A similar type of fibrosis was evident in the surrounding fat. Throughout the artery were a few lymphocytes, neutrophils and eosinophils. A small arteriole in the adventitia showed similar fibrosis and infiltration in the wall. Several small subcutaneous vessels showed perivascular collections of lymphocytes. Stains for elastic tissue demonstrated the fraying and breaking up of the elastica interna. The elastic tissue was decreased in amount.

A final biopsy specimen, taken after the subsidence of the disease through an area of skin and muscle known to have been previously involved, showed no significant pathologic features.

Case 2.—M. D., a white girl of 15, experienced lower abdominal pain on the right side followed by nausea, vomiting and a sensation of chilliness. The illness was of one week's duration when the patient was admitted to the hospital.

The physical examination showed tenderness in the right lower quadrant of the abdomen. The blood pressure was 110 systolic and 70 diastolic. The leukocyte count was 8,000.

An appendectomy was performed, and convalescence was uneventful. Eleven years after discharge (at the time of this report), the patient had remained well.

Microscopic Examination.—Sections of the appendix showed small arteries with fibrinoid necrosis of the wall. Associated was periarterial infiltration with plasma cells, lymphocytes and neutrophils. Some vessels showed infiltration of the wall with a similar type of exudate. An occasional artery was occluded by granulation tissue in which a few neutrophils, plasmocytes and lymphocytes could be seen.

REVIEW OF CASES IN THE LITERATURE

A number of cases of periarteritis nodosa reported in the literature are of special interest because of the course of the disease. Chronicity with periods of remission of many years' duration and instances of recovery have been reported. Cases in which recovery occurs are often difficult to evaluate; in a disease that shows remissions and exacerbations so frequently, the permanence of recovery must be questioned unless a long follow-up study is made. In the unusual case reported in this paper (case 1), the disease reappeared after a period of twelve years.

The average duration of life following the onset of symptoms is under one year. Gruber,[21] in 1926, reported the average duration in 57 cases to be 4.7 months. Curtis and Coffey,[8] reporting on 17 cases, obtained an average of sixteen months; Strong,[7] reporting on 21 cases, computed an average of five months, and Harris, Lynch and O'Hare,[11] summarizing 101 cases found the average duration to be 8.6 months.

21. Gruber, G. B.: Kasuistik und Kritik der Periarteritis Nodosa, Zentralbl. f. Herz.- u. Gefässkr. **18**:145, 1926.

Representative case reports have been abstracted from the literature to illustrate chronicity as well as recovery. Table 3 contains reports of cases with chronic courses, i. e., illnesses of many years' duration with persistent symptoms or periods of remission and exacerbation.

Since periods of remission are common in the course of the disease, cases in which recovery occurred are arbitrarily separated into two groups depending on whether an observation period of at least one year was reported. Table 4 lists the cases in which recovery was reported with short follow-up periods. Cases of periarteritis nodosa in which the patients were reported as recovered with a follow-up period of one year or more are briefly summarized.

TABLE 3.—*Reported Cases of Periarteritis Nodosa with Chronic Courses*

Author	Patient		Course
	Sex	Age, Years	
Schmorl (Verhandl. d. deutsch. path. Gesellsch. **6**: 206, 1903)	F	53	Patient died after 2 years, acute portal thrombosis; only healed lesions of arteritis found at autopsy
Arkin (Am. J. Path. **6**: 401 [July] 1930)	M	..	Patient died after 4 years, myocardial and renal insufficiency; histologic studies showed healed end stages of periarteritis nodosa
Macaigne and Nicaud (Presse méd. **40**: 665 [April 27] 1932)	F	27	Initial attack followed by latent period of 5 years with crises for next 10 years
Grant [12]	F	17	Periodic attacks for 8 years with active disease at end of period
Miller and Daley [13]	M	14	Chronic course of 8 years' duration with disease reported active at end of period
	M	40	Recurrent attacks for 5½ years with active disease at end of period
Galán (Bol. Soc. cubana de pediat. **17**: 293 [Aug.] 1945)	M	9	Recurrent episodes over 4 years with evidence of activity at end of period
King (J. Mt. Sinai Hosp. **15**: 97 [July-Aug.] 1948)	F	51	Duration of 2 to 3 years with evidence of activity at end of period

Erlandsson.[22]—This white patient died one year after the diagnosis of periarteritis nodosa had been established by biopsy. At necropsy, no lesions of the disease were observed. Death was due to metastases from carcinoma of the uterus.

Lindberg.[23]—A white boy of 15 had been sick for a period of four years. Biopsy of subcutaneous nodules established the diagnosis. At the time of publication of the report, the patient had been entirely well for one year.

Harris, Lynch and O'Hare.[11]—A student of 19, of Greek extraction, had a past history of painful joints and loss of weight of five months' duration. An examina-

22. Erlandsson, S.: Neurologische Krankheitsbilder bei Periarteritis nodosa, Acta psychiat. et neurol. **6**:369, 1931.

23. Lindberg, K.: Ueber eine subkutane Form der Periarteriitis nodosa mit langwierigem Verlauf, Arb. a. d. path. Inst. d. Univ. Helsingsfors **7**:159, 1933.

tion had revealed diffuse tenderness of the muscles, hepatomegaly, splenomegaly, fever, tachycardia and a leukocyte count of 18,400. Transitory subcutaneous nodules had appeared. After three months, there was considerable improvement in the patient's condition. Seven months later, similar symptoms of generalized weakness and pain and tenderness of the muscles reappeared. Numerous erythematous circinate lesions appeared on the trunk and extremities. Biopsy established the diagnosis. The patient improved and when seen four years after the onset of the symptoms he was perfectly well.

Grant.[12]—A white engineer of 61 had a previous history of asthma of seven years' duration. Pain and pallor in the fingers of the left hand had developed on

TABLE 4.—*Reported Cases of Periarteritis Nodosa in Which Patients Recovered but Subsequent Observation Lasted Less Than One Year*

	Patient		
Author	Sex	Age, Years	Course
von Haun (Virchows Arch. f. path. Anat. **227**: 90, 1919)	M	30	Patient ill 3 months; returned to duty as soldier
Carling and Hicks (Lancet **1**: 1001 [May 19] 1923)	M	30	Patient returned to work asymptomatic 9 months after onset
Schottstaedt (California & West. Med. **36**: 186 [May] 1932)	M	41	Two episodes separated by period of 2 months; 1 month after second attack, patient asymptomatic and returned to work
Motley (J. A. M. A. **106**: 898 [March 14] 1936)	M	31	Single severe protracted course; patient returned to work 10 months after discharge
Vining (Arch. Dis. Childhood **13**: 31 [March] 1938)	F	7	Recurrent attacks over 2 years; patient entirely asymptomatic at end of period
Grant [12]	M	38	Illness of 5 months' duration; except for residual palsies, patient well 5 months later
	M	45	Patient returned to work 1 month after onset of illness; remained in good health 8 months later
Miller and Daley [13]	M	28	Patient severely ill for 3 months; 7 months later reported entirely well
White (Minnesota Med. **30**: 303 [March] 1947)	F	73	Patient hospitalized three times in 16 months; entirely asymptomatic 6 months after discharge

exposure to cold. A single subcutaneous nodule had appeared on the dorsum of the left forearm and gradually subsided. Two years later, there appeared pain, weakness and sensory changes in the left arm and abdominal distention and tenderness. The asthma increased in severity. Subcutaneous nodules appeared on the left upper extremity, and biopsy of one of them established the diagnosis. Improvement followed, and three years after the onset of the first symptom the patient was at work. He remained well.

Goldman, Dickens and Schenken.[24]—A Negro of 22 gave an initial complaint of weakness and dull, aching muscular pain and tenderness. There followed chills, fever, abdominal pain, loss of weight and the appearance of subcutaneous nodules.

24. Goldman, B. A.; Dickens, K. L., and Schenken, J. R.: The Apparent Cure of Periarteritis Nodosa with Sulfapyridine, Am. J. M. Sc. **204**:443 (Sept.) 1942.

Biopsy of a nodule established the diagnosis. A total of 156 Gm. of sulfapyridine was given in thirty-two days; improvement followed. Nineteen months after discharge, the patient was in excellent health, performing manual labor.

MacKeith.[25]—A white engineer of 27 had a history of chronic cough. A sudden onset occurred, including pain in the right groin, right hemiparesis, localized edema of the right arm and the appearance of two subcutaneous nodules on the right calf. Leukocytosis was present (the count was 12,000, with a normal differential count). Pyrexia and tachycardia were present. Histologic examination of a subcutaneous nodule established the diagnosis. Five weeks after admission, the patient left the hospital quite well. Two and one-half years later he was reportedly asymptomatic.

A white engineer of 58 gave a history of recurrent bronchitis of two years' duration. The sudden onset of paresis of the hands, legs and feet was associated with sensory changes. Pitting edema of the upper extremities and the ankles was present. The value for blood urea nitrogen was elevated to 70 mg. per hundred cubic centimeters, and albuminuria was present. Diarrhea appeared, and the muscular weakness increased in severity; wasting was severe. By the second month, improvement was noted. Six months later, the patient was ambulatory but both hands were wasted and contracted. One year later, the patient could write, shave and walk a mile.

Contratto.[26]—A Chinese of 40, with a past history of pulmonary tuberculosis experienced fever, malaise and swelling of the right side of the neck; nodules appeared on the right forearm. Biopsy of a nodule established the diagnosis of periarteritis nodosa. Improvement followed, and the patient returned to work at the end of three months. After nine months of good health, he became ill once more for four months. An interval of two years of good health was followed by fever, enlargement of the posterior cervical lymph nodes, pains in the legs, loss of weight and appearance of subcutaneous nodules. Biopsy of a subcutaneous nodule again demonstrated active periarteritis nodosa, whereas a cervical lymph node showed active tuberculosis. At the end of four months, the patient felt well. Two years later, on examination, he was found to be entirely normal.

Goodman.[27]—A white student of 17 was given sulfadiazine for a sore throat. Six weeks later, the soreness appeared again. The patient became seriously ill after two days of sulfadiazine therapy, and use of the drug was discontinued. An erythematous skin rash appeared and progressed, to become purpuric. Fever, muscular pain and migratory swelling and pain in the joints appeared. The blood pressure rose to 164 systolic and 104 diastolic. Hematuria and loss of weight were noted. The white cell count ranged from 10,300 to 19,900 and the platelet count from 76,000 to 147,000. Biopsy of the left deltoid muscle established the diagnosis. Inadvertently, sulfadiazine was administered again; in spite of the development of

25. MacKeith, R.: Localized Subcutaneous Oedema with Weakness of Limb Muscles: Syndrome Due to Polyarteritis Nodosa, Brit. M. J. **1**:139 (Jan. 29) 1944.

26. Contratto, A. W.: Periarteritis Nodosa: A Report of Two Cases, One with Special Reference to Sensitivity Factors, Arch. Int. Med. **80**:567 (Nov.) 1947.

27. Goodman, M. J.: Periarteritis Nodosa with Recovery: Report of an Unusual Case Apparently Due to Sensitivity to Sulfadiazine, Ann. Int. Med. **28**:181 (Jan.) 1948.

an urticarial rash, it was continued. One week later, improvement was noted and the temperature became normal. Twenty-eight months later, the patient was in good health.

ETIOLOGY

Most evidence at the time of writing supports the experimental view that periarteritis nodosa represents a nonspecific hypersensitivity reaction to many agents. Gruber [5] suggested early that periarteritis nodosa might result from a hyperergic reaction of the arteries to the various infectious or damaging agents. The role of bacterial antigens has been stressed. Of the instances reported, many were preceded by a respiratory infection, erysipelas, scarlet fever, tuberculosis or syphilis. The disease has followed the administration of antipneumococcus serum. The lesions have been produced experimentally by the administration of the sulfonamide drugs, organic arsenicals, desoxycorticosterone, iodine, thiourea and other substances.

PATHOLOGY

The disease produces cellular infiltration, necrosis, aneurysms and thrombosis of blood vessels. It involves segments of arterioles, small, medium and large arteries and, very rarely, veins. Usually many organs, systems or tissues are affected simultaneously. Evidences of acute, subacute and fibrosing stages may be present at any one time.

Microscopic study of the lesions initially shows an acute injury of varying severity involving the vessel wall. When necrosis or severe damage to the vessel wall exists, reparative fibrosis may follow. Thrombosis is common and the formation of aneurysms the exception. The degree of necrosis and thrombosis determines the functional state of the involved vessel, both during the acute phase and subsequently. In those lesions in which thrombosis and necrosis are absent, there may be complete healing. Usually the thrombosed or severely injured artery does not regain its full function.

The pathologic process appears to begin as edema of the vessel wall. This is followed by a fibrinoid degeneration of the media, destruction of the elastic laminas and infiltration of the perivascular region with inflammatory cells. The necrotic tissue is replaced by granulation tissue, and the acute inflammatory exudate, by a subacute and chronic exudate of histiocytes, lymphocytes and plasma cells. If thrombosis has occurred, organization with recanalization may follow. The weakened vessel wall may give way, with the formation of aneurysms or with hemorrhage. In the healed stage, there is frequently thickening of the arterial wall due to intimal proliferation and subintimal, medial and periadventitial fibrosis.

Localized periarteritis nodosa, or disease confined to a single organ, presents the same histologic picture as the generalized form. At the time of this report, there is little evidence in favor of classification of the generalized and localized types as different pathologic states.

RECOVERY

Periarteritis nodosa need not result in death. The natural history of the disease evolves from an initial degenerative and inflammatory phase to those of granulation and healed granulation. The histologic changes, therefore, show a progression toward healing.

The duration of the illness and its ultimate outcome are closely correlated with the degree of involvement of vital organs and the resultant impairment of function of these organs. Mild cases of periarteritis nodosa with minimal pathologic changes undoubtedly exist. Clinically, the manifestations are difficult to recognize when mild; the disease may thus go undiagnosed. As an exacerbation in a known case, minimal changes have been noted.

Healing may occur clinically as well as histologically when the disease is confined primarily to nonvital organs or tissues. When extensive involvement of the renal, pulmonary, cardiac or intra-abdominal arteries occurs, the mortality is great. In those instances, however, in which the peripheral arteries supplying nonvital structures are mainly involved, recovery may be expected.

On both admissions, involvement predominantly of the peripheral arteries was noted in case 1. The course was febrile, with pronounced leukocytosis, polymyositis and cutaneous manifestations. Complete recovery followed each episode. A period of twelve years of good health intervened between admissions.

Recovery in cases with extensive involvement of vital structures occasionally occurs. However, death may follow as a result of the histologic healing causing vascular insufficiency of such organs as the heart, kidneys or liver.

Periarteritis may involve any organ; cases have been reported in which the process was local and not general. Spiegel[10] reported 2 cases in young people in which the appendix alone was involved. In both, recovery was uneventful. Powell and Pritchard[28] reported a case in which the disease involved one kidney. Nephrectomy was performed because of hematuria. Ten months after the onset of symptoms, the patient was well and had returned to work.

28. Powell, R. E., and Pritchard, J. L.: Periarteritis Nodosa, with Report of Case Involving One Kidney, Brit. J. Urol. **4**:317 (Dec.) 1932.

M. D., the patient in case 2, recovered from an appendectomy and remained well eleven years later. Microscopic examination of sections of the appendix showed lesions indistinguishable from those seen in the more generalized form of periarteritis nodosa.

THERAPY

During the acute phase, treatment must be mainly supportive. Since pain is frequently severe, sedation and the liberal use of analgesics are indicated. The maintenance of proper nutrition is important. The disease is a wasting one, and its course may be protracted. Flexion deformities occur, and unless proper orthopedic appliances are used and correct physical therapy is instituted, loss of function may result.

Although the causation is still unknown, there is good reason to suspect a hypersensitivity reaction. Early recognition and removal of the antigenic agent would be indicated. A history of drug sensitivity or the use of some medication prior to the onset of the disease should be regarded with suspicion. The antibiotic drugs may be of vlaue when the antigenic agent is bacterial.

After recovery, hygienic measures for the prevention of infection should be instituted. The early recognition and vigorous therapy of an established infection are important. The removal of foci of infection in the case of a patient protected by the prophylactic administration of penicillin would appear to be indicated.

Any cures in periarteritis nodosa ascribed to various drugs must be viewed with suspicion, since the natural course of the disease may be one of remissions and exacerbations. During the early phase of the second admission in case 1, an antihistaminic agent was used. No conclusions are justifiable as to its value at this time.

SUMMARY AND CONCLUSIONS

Two unusual cases in which recovery took place are reported. The patient in case 1 had two histologically proved episodes of periarteritis nodosa separated by an interval of twelve years. One year after discharge from the second hospitalization, the patient was entirely asymptomatic. The patient in case 2, who had localized periarteritis of the appendix, was well eleven years after discharge.

The literature is reviewed to illustrate chronicity as well as recovery in periarteritis nodosa. The etiology and pathology are discussed, and suggestions for therapy are presented.

Periarteritis nodosa is not invariably an acutely fatal disease. The course may be chronic with periods of remission and exacerbation. Recovery may occur.

Recovery may be expected under the following circumstances: confinement of the disease predominantly to nonvital structures; minimal involvement of organs followed by healing, and localization of the disease to part of a single organ.

Recovery can occur despite the involvement of vital structures, but death may follow in the inactive phase many years later from vascular insufficiency to such organs as the heart, kidneys or liver.

NOTE.—At the time of publication it is well over two years since J. Mc.C. (case 1) was discharged from hospital. He remains in good health.

Dr. Dante Campagna-Pinto, Assistant in Pathology at the Mallory Institute of Pathology, Boston City Hospital, supplied the descriptions of the microscopic sections.

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CORONARY HEART DISEASE AND XANTHOMA TUBEROSUM ASSOCIATED WITH HEREDITARY HYPERLIPEMIA

Study of Thirty Affected Persons in a Family

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CLINICAL investigations concerning disturbances in lipid metabolism have opened a new chapter in the etiology of coronary heart disease. Recent studies have revealed an extremely high incidence of xanthomas and specific types of heart disease associated with hyperlipemia, especially hypercholesteremia.

The earlier investigators were concerned mainly with the etiology of xanthomatous lesions of the skin and tendons. These deposits have long been considered medical curiosities, and even today little is known concerning their formation. Tuberous xanthomas were first described by Addison and Gull,[1] in 1851, but it was not until 1920 that Chauffard, Laroche and Grigaut [2] and Burns [3] demonstrated that there was an increased amount of total serum cholesterol in patients with xanthomas. In 1929, Wile, Eckstein and Curtis [4] stated that the formation of xanthomas could not be explained solely by the theory of hypercholesteremia and that a defect in fat metabolism, in which cholesterol undoubtedly played a part, was apparently responsible.

In general, patients having xanthomas of tendons and tendon sheaths have an elevated number of blood lipids, especially serum cholesterol. Occasionally one sees these lesions in the absence of hypercholesteremia,

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1. Addison, T., and Gull, W.: On a Certain Affection of the Skin: Vitiligoidea —α, Plana, β, Tuberosa, Guy's Hosp. Rep. **7**:265-276, 1851.

2. Chauffard, A.; Laroche, G., and Grigaut, A.: La cholestérinémie à l'état normal et pathologique, Ann. de méd. **8**:69-91 (Aug.) 1920; Le cycle de la cholestérine dans l'organisme, ibid. **8**:149-172 (Sept.) 1920; Les dépôts locaux de cholestérine rapports entre la cholestérine circulante et la cholestérine fixée, ibid. **8**:321-334 (Nov.) 1920.

3. Burns, F. S.: A Contribution to the Study of the Etiology of Xanthoma Multiplex, Arch. Dermat. & Syph. **2**:415-429 (Oct.) 1920.

4. Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Lipid Studies in Xanthoma, Arch. Dermat. & Syph. **19**:35-51 (Jan.) 1929.

but Boas and others [5] stated the belief that xanthomas are associated with hypercholesteremia at some stage during their development. In 1893, Török [6] recognized the familial tendency of tuberous xanthomas and made an extensive study of the literature concerning the various aspects of xanthomas. Since then, approximately thirty papers have reported tuberous xanthomas in 2 or more members of a family.

There has been some discord as to the genetic transmission of this supposed trait because of its sporadic occurrence within families involved. Levin and Sullivan [7] stated that tuberous xanthomas are inherited as a recessive trait. They stated: "The condition is transmitted as a recessive characteristic and may be inherited through either parent." This opinion on genetic transmission is not in agreement with the general consensus, which is that a trait transmitted as an autosomal recessive character must be through both parents. I have studied all the available case reports of familial tuberous xanthomas and have been unable to find data on any family in which xanthomas could be interpreted as having been transmitted by autosomal recessive factors. Thannhauser and Magendantz,[8] Müller,[9] Cockayne [10] and other authors have stated the belief that tuberous xanthomas are transmitted as a dominant mendelian trait.

Basically, the inherited defect is one of lipid metabolism or, more specifically, of cholesterol metabolism; the occurrence of xanthoma tuberosum, angina pectoris, arcus senilis, xanthelasma and atheroma is a complication or variation of the disease. This theory is substantiated by the case reports in the present paper. Müller,[9b] Boas and others,[11] Wile and Duemling [12] and others reported similar findings.

5. Boas, E. P.; Parets, A. D., and Adlersberg, D.: Hereditary Disturbance of Cholesterol Metabolism: A Factor in the Genesis of Atherosclerosis, Am. Heart J. **35**:611-622 (April) 1948.

6. Török, L.: De la nature des xanthomes avec quelques remarques critiques sur la notion des tumeurs, Ann. de dermat. et syph. **4**:1109-1156, 1893.

7. Levin, A. L., and Sullivan, M.: Familial Xanthoma: Report on Three of Five Siblings with Xanthoma Tuberosum Multiplex, Arch. Dermat. & Syph. **33**: 967-969 (June) 1936.

8. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, Ann. Int. Med. **11**:1662-1746 (March) 1938.

9. (*a*) Müller, C.: Xanthomata, Hypercholesterolemia, Angina Pectoris, Acta med. Scandinav., 1938, supp. 89, pp. 75-84; (*b*) Angina Pectoris in Hereditary Xanthomatosis, Arch. Int. Med. **64**:675-700 (Oct.) 1939.

10. Cockayne, E. A.: Inherited Abnormalities of the Skin and the Appendages, New York, Oxford University Press, 1933.

11. Boas, Parets and Adlersberg.[5] Boas, E. P., and Adlersberg, D.: Familial Hypercholesterolemia (Xanthomatosis) and Atherosclerosis, J. Mt. Sinai Hosp. **12**:84-86 (May-June) 1945.

12. Wile, U. J., and Duemling, W. W.: Familial Xanthoma, Arch. Dermat. & Syph. **21**:642-647 (April) 1930.

Stecher and Hersh [13] analyzed mathematically the reports of hereditary disturbances of cholesterol metabolism reported by Boas and his co-workers [5] and stated: "We are thus led to the conclusion that hypercholesterolemia is an autosomal dominant trait with complete or nearly complete penetrance."

Arcus senilis [14] (arcus lipoides) and xanthelasma are frequently seen in patients with hypercholesteremia. Montgomery and Osterberg [15] stated that the histologic picture and the hyperlipemia in cases of xanthelasma strongly suggest that xanthelasma is an accompaniment of systemic disease and is simply a variation of one of the types of xanthoma. Barker [16] and Montgomery [17] reported cases of occlusive arterial disease of the lower extremities associated with hyperlipemia and xanthoma tuberosum. Literature on this subject is sparse.

There are many reports in the literature showing that xanthomatous lesions may occur on the heart valves and in other structures of the heart so as to hamper its efficiency greatly. As early as 1873, Fagge [18] stated:

> . . . The nature of the growth [xanthoma] appears to be a kind of universal atheromatous change and is essentially the same wherever it occurs. . . . It will thus be seen that the condition is exactly parallel to that found in the early stages of atheromatous degeneration of the arteries.

But only during the last two decades has much emphasis been placed on the relationship of xanthoma tuberosum, hypercholesteremia and coronary heart disease.

Török [6] (1893) reported cases in which death was due to xanthomatous changes in the cardiovascular system of patients with cutaneous xanthoma. In 1913, Anitschkow and Chalatow [19] produced lesions which resembled the atherosclerotic plaques of the human being by

13. Stecher, R. M., and Hersh, A. H.: Note on the Genetics of Hypercholesterolemia, Science **109**:61-62 (Jan. 21) 1949.

14. Klatskin, G.: Familial Xanthomatosis and Arcus Senilis, Internat. Clin. **3**:13-39 (Sept.) 1941.

15. Montgomery, H., and Osterberg, A. E.: Xanthomatosis: Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch. Dermat. & Syph. **37**:373-402 (March) 1938.

16. Barker, N. W.: Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, Ann. Int. Med. **12**:1891-1895 (May) 1939.

17. Montgomery, H.: Xanthomatosis: A Systemic Disease, Proc. Staff Meet., Mayo Clin. **12**:641-644 (Oct. 13) 1937.

18. Fagge, C. H.: General Xanthelasma or Vitiligoidea, Tr. Path. Soc. London **24**:242-250, 1872-1873.

19. Anitschkow, N., and Chalatow, S.: Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse, Centralbl. f. allg. Path. u. path. Anat. **24**:1-9 (Jan. 15) 1913.

feeding rabbits cholesterol. That observation was confirmed by Bailey,[20] Leary [21] and others. Stocks [22] stated that a conservative estimate of the incidence of atherosclerosis of the coronary arteries in patients with angina pectoris is 85 per cent.

The physiologic role played by cholesterol in the human body is still poorly understood. It is a constituent of all animal tissues, but the nature of its metabolism and synthesis remains unproved. Montgomery and Osterberg,[15] Thannhauser and Magendantz [8] and Gubner and Ungerleider [23] recently reported detailed studies and quoted extensive literature concerning cholesterol and other lipid substances in relation to their clinical, histopathologic and chemical significance.

Recent papers have reported a high incidence of disturbances in blood lipid metabolism in patients suffering from coronary heart disease. Mjassnikow [24] reported on 16 patients with atherosclerosis, 12 of whom had angina pectoris. The serum cholesterol level was elevated in all. Davis and his co-workers [25] found that the levels for total cholesterol, free fatty acids and lipid phosphorus were higher among 59 patients with angina pectoris than in a comparable group of controls. Twenty-two of the 28 young patients with disease of the coronary arteries reported on by Lerman and White [26] had serum cholesterol values above 250 mg. per hundred cubic centimeters. Boas and others,[5] Steiner and Domanski,[27] Underdahl and Smith,[28] Yater and his associates [29] and many others reported similar findings. Laliberté and Vachon [30] and

20. Bailey, C. H.: Atheroma and Other Lesions Produced in Rabbits by Cholesterol Feeding, J. Exper. Med. **23**:69-85 (Jan.) 1916.

21. Leary, T.: Experimental Atherosclerosis in the Rabbit Compared with Human (Coronary) Atherosclerosis, Arch. Path. **17**:453-492 (April) 1934.

22. Stocks, P.; in Cowdry, E. V.: Arteriosclerosis: A Survey of the Problem, New York, The Macmillan Company, 1933, chap. 7.

23. Gubner, R., and Ungerleider, H. E.: Arteriosclerosis: A Statement of the Problem, Am. J. Med. **6**:60-83 (Jan.) 1949.

24. Mjassnikow, A. L.: Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, Ztschr. f. klin. Med. **102**:65-78, 1925.

25. Davis, D.; Stern, B., and Lesnick, G.: Lipid and Cholesterol Content of Blood of Patients with Angina Pectoris and Arteriosclerosis, Ann. Int. Med. **11**:354-369 (Aug.) 1937.

26. Lerman, J., and White, P. D.: Metabolic Changes in Young People with Coronary Heart Disease, J. Clin. Investigation **25**:914 (Nov.) 1946.

27. Steiner, A., and Domanski, B.: Serum Cholesterol Level in Coronary Arteriosclerosis, Arch. Int. Med. **71**:397-402 (March) 1943.

28. Underdahl, L. O., and Smith, H. L.: Coronary Artery Disease in Women Under the Age of Forty, Proc. Staff Meet., Mayo Clin. **22**:479-482 (Oct. 15) 1947.

29. Yater, W. N., and others: Coronary Artery Disease in Men Eighteen to Thirty-Nine Years of Age, Am. Heart J. **36**:481-526 (Oct.) 1948.

30. Laliberté, H., and Vachon, M.: Infarctus du myocarde et cholestérol (Rapport préliminaire), Laval méd. **13**:294-302 (March) 1948.

Welin [31] reported on a total of 192 patients with myocardial infarction, most of whom had hypercholesteremia.

In 1910, Arning [32] reported xanthoma tuberosum in a mother and 4 of her 9 children. All 5 affected persons had heart disease. Similar reports have been made in the past, but not until recently have familial defects in the metabolism of the lipids been recognized as an important cause of heart disease. The reports of Lane and Goodman,[33] Montgomery and Osterberg,[15] Müller [9b] and others have apparently brought about this recognition. Boas and others [8] suggested that families with xanthoma may represent only the extremes of disturbed cholesterol metabolism and that many patients with apparently uncomplicated disease of the coronary arteries might fall into a similar pattern. Investigation into the problem has been greatly hampered because of the lack of opportunity to study families large enough to indicate the specific type of genetic transmission of the metabolic defect and, thus, to allow a

TABLE 1.—*Cholesterol Values in a Patient with Coronary Arteriosclerosis*

Date	Total Serum Cholesterol, Mg./100 Cc.	Comment
1/28/49	340	
2/ 7/49	340	
2/10/49	338	Sample obtained 24 hours after ingestion of 2 Gm. cholesterol with 50 cc. 20 per cent alcohol
2/14/49	318	
2/18/49	300	
2/25/49	168	
2/25/49	238	Sample obtained 4 hours after ingestion of 50 cc. choline bicarbonate
2/26/49	224	Sample obtained 24 hours after ingestion of the choline

better understanding of it. Other difficulties encountered are in the quantitative determination of total lipids and serum cholesterol in affected persons. There is little deviation in the cholesterol level of normal persons, whereas a wide fluctuation is well known to exist in consecutive determinations in affected persons. Steiner and Domanski [27] showed that patients with coronary arteriosclerosis had much greater fluctuations in cholesterol levels from month to month than did controls. This has has also been noted in my studies; the following case report is illustrative:

A woman of 31 had extremely large tuberous xanthomas over the heels, knees, back and dorsum of the hands (she was not a member of the family reported on later in this paper). The serum cholesterol values are listed in table 1.

31. Welin, G.: Serum Cholesterol in Cardiac Infarctions, Nord. med. **37:** 324-326 (Feb. 13) 1948.

32. Arning, E.: Ein Fall von familiärer Xanthomatose; abstracted, Arch. f. Dermat. u. Syph. **105:**290-291 (Oct. 26) 1910.

33. Lane, C. G., and Goodman, J., Jr.: Xanthoma Tuberosum: Report of Familial Occurrence with Probable Cardiac Lesions, Arch. Dermat. & Syph. **32:** 377-384 (Sept.) 1935.

During the period of observation, there were no changes in the patient's dietary habits or environment, but on February 25 there was a sudden drop of 50 per cent in the total serum cholesterol.

Thus, a normal serum cholesterol level determined from a single blood sample does not necessarily exclude a person from the group having hypercholesteremia. McGraw [34] stated the belief that determinations of blood cholesterol or blood lipids alone are of little value in the study of patients with xanthomatous lesions. Samples should be obtained from patients in the fasting state and analyzed as soon as possible for total serum lipids and cholesterol. The quantitative determinations of the various components of the blood lipids are of value, and the analysis of the relative amounts of these constituents may in the future lend much to a better understanding of this problem.

REPORT ON FAMILY

Pedigrees of two families, members of which intermarried in one instance, are presented graphically in figure 1. There was a definite familial tendency toward heart disease in family B and complete absence of any type of heart disease in family A. Both families were orginally of Northern European stock. They belonged to the same religious sect (Latter-Day Saints) and so lived rather similar lives. Generations I and II of both families had migrated to the Rocky Mountains and helped to settle the communities in which they lived.

Family A.—I was able to obtain information concerning this family dating to 1743. It was impossible to ascertain the cause of death for those members living many years ago, but the age of death for the principal members shows the high incidence of longevity among them. As will be noted, in family B the age of death was almost uniformly in the fifth or sixth decade of life, whereas several members of family A lived to be over 85. Information was exact as to the day and year of birth and death for nearly all persons; specific vital statistics were available for the following:

I-1: This woman was born in 1802; the date of death was unknown. She was delivered of 10 children (7 males and 3 females).

II-2: This man was born in 1799 and died at 77. His father was born in 1743; the date of his death is uncertain. However, several siblings were known to be younger than subject I-2.

II-1: The second wife of subject II-3 was born in 1847 and died at 73. She was delivered of 7 children (4 males and 3 females). Two male children were still living at the time of writing. One was 89, the other 85.

II-2: The third wife of subject II-3 was born in 1843 and died at 79. She was delivered of 5 children (4 males and 1 female). The male children died at the ages of 57, 72, 75 and 78; the daughter was still living at 81.

34. McGraw, A. B.: Juvenile Xanthoma Multiplex: Case Report and Discussion of the Literature, Am. J. Cancer **18**:345-356 (June) 1933.

II-3: This man was born in 1823 and died at 57.

II-4: The first wife of subject II-3 was born in 1822 and died at 65. She had several brothers and sisters who lived to that age.

III-1 to III-8: These subjects died at the following ages: birth, 57, 11, 64, 22 (malaria ?), 38 (pneumonia), 30 (pneumonia) and 58.

III-9: This man, born in 1861, died at 82 of cancer of the stomach.

The descendants of the wives of subject II-3 numbered into the hundreds. I was unable to find any history of a familial type of heart disease or of xanthoma in them except in the descendants of subject III-9, who married into family B.

Family B.—I was able definitely to establish a high incidence of heart disease, xanthoma tuberosum, angina pectoris and hyperlipemia in five, and possibly six, generations of this family. Although both

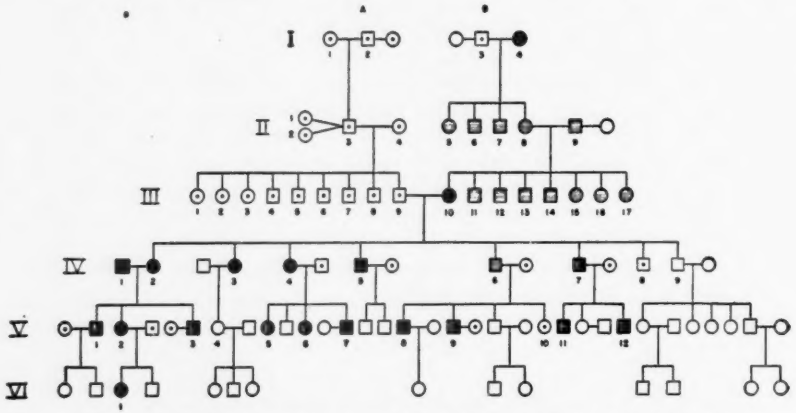

Fig. 1.—Pedigree chart of two unrelated families, members of which intermarried in one instance. Family A was normal in all respects; family B showed a high incidence of heart disease, xanthomas and hyperlipemia. The square symbols designate males, and the round symbols, females. The symbols with black dots represent normal persons, and the plain figures indicate persons not examined or for whom no history could be obtained. The solid black symbols designate persons with xanthoma tuberosum, angina pectoris and hyperlipemia occurring together. (Additional material in the text concerns subjects III-10, IV-3 and IV-5.) The half-solid symbols represent subjects with hyperlipemia.

family A and family B lived in an area endemic for rheumatic heart disease, apparently few persons, if any, in either family became afflicted with the disease. I found only 1 instance (that of subject I-3) of a person's living past 65 in this family. According to the history obtained, all persons in the first three generations of this family except subject I-3 died of heart disease. The following data were obtained:

Generation I: I-3: It was estimated by persons in generation IV that the subject died in his eighties (cause unknown).

I-4: This woman was presumably the original person in this pedigree transmitting the trait. It is believed that she died of heart disease in "midlife."

Generation II: II-5: This woman died suddenly of "heart disease" in "midlife."

II-6: This man died of "heart disease" at a "young age."

II-7: This man died of "heart disease" in his fifties.

II-8: This woman died suddenly at 65 after a heart attack.

II-9: This man died of heart trouble in his sixties. Several siblings of his second wife were known to have heart disease.

There were several additional siblings of subjects I-3 and I-4 who are not graphically represented in the pedigree chart because of lack of information concerning them. It was well known in the community that most of these siblings and many of their descendants had heart disease. Local physicians would tell members of generation III that they were afflicted with "one of those [family name] hearts."

Generation III: III-10: The subject died at 57 of cancer of the stomach. She had xanthoma tuberosum of the achilles tendons, arcus senilis and a long history of angina pectoris.

III-11: The subject died suddenly at 45 of heart disease. He suffered from several attacks of angina pectoris.

III-12: This man died at 60 after many years of heart trouble.

III-13: This man died suddenly at 46 after severe pain in the chest. The history revealed several attacks of angina pectoris.

III-14: This man died at 51 after many years of heart trouble.

III-15: This subject died at 51 of heart disease. She had "dropsy" for some time before death.

III-16: The subject died suddenly at 50 of a heart attack. She suffered from angina pectoris.

III-17: The subject died at 50 of heart disease. She had "dropsy" before death.

There were 4 additional siblings in generation III who are not represented graphically in the pedigree chart because of lack of information concerning them. Subjects III-11 to III-17 had over 250 descendants, most of whom were available for study. However, I was unable to undertake a task of such scope.

Generation IV: IV-1: This man died suddenly of coronary occlusion at 47. One brother also died of coronary occlusion, at 48.

IV-2: The patient, a woman of 62, was first seen at the Stanford University Hospitals because of a history of severe pain of several years' duration in the lower portion of the back. The condition was diagnosed as lumbosacral arthritis, for which a spinal fusion was performed on Jan. 31, 1949. The studies concerning xanthomas, disturbances in lipid metabolism and angina pectoris were made because of interest in this subject and were incidental to the presenting orthopedic problem.

The patient had four attacks of severe substernal pain in twelve years, the last occurring on March 28. The administration of glyceryl trinitrate completely eliminated the pain in the chest. The patient often became dyspneic on exertion. The tuberous xanthomas of the achilles tendons were first noted when she was 37. Xanthelasma and arcus senilis had been present "only for the past few years."

The blood pressure was 130 systolic and 80 diastolic. Arcus senilis and xanthelasma of the right upper eye lid were noted. The heart was not enlarged; there were no thrills or murmurs, and the rhythm was regular. The peripheral blood vessels were soft. Lesions of xanthoma tuberosum (6 mm. in diameter) were located on the extensor tendons of the index fingers; fusiform tuberous xanthomas 10 by 4.5 cm., were located within the distal portion of the achilles tendons.

Blood values were as follows: red blood cells, 5,050,000; hemoglobin, 15.5 Gm. per hundred cubic centimeters; packed cell volume, 38 per cent; sedimentation rate,

Fig. 2.—Photomicrograph of biopsy specimen of lesion of xanthoma tuberosum from left achilles tendon of subject IV-2. Dense bands of collagen are prominent, and there are numerous fibroblasts. Occasional polymorphonuclear leukocytes lie outside the capillary walls. A number of large, pale-staining foam cells are present. The diagnosis was xanthoma and foreign body reaction of the achilles tendon.

30 mm. in one hour, and white blood cells, 9,500 (polymorphonuclear leukocytes 58 per cent, lymphocytes 42 per cent). The urine was normal.

An electrocardiogram made on January 31 showed left axis deviation but was otherwise normal. The Wassermann and Hinton reactions were negative. Biopsy of a mass on the left achilles tendon, diagnosed as a xanthoma (fibroxanthoma), gave a foreign body reaction (fig. 2). Blood chemistry values are given in table 2.

IV-3: The patient was a woman of 58. She had had severe attacks of angina pectoris for the past twenty years; glyceryl trinitrate eliminated pain in the chest. At the age of 55, she had had a sudden, excruciating pain in the chest; electrocardiograms reportedly suggested myocardial damage at that time. Large tuberous xanthomas were noted on the extensor tendons of the hands and on the achilles tendons, and xanthelasma and arcus senilis were present. The onset of the tuberous xanthomas of the achilles tendons had been in the patient's early twenties. The xanthomas were occasionally painful. When she was 30, a thyroidectomy was performed at the Mayo Clinic. On examination, the heart was found to be normal; the basal metabolic rate was +38, and no lipid studies were made. The following is a summary of information concerning the "swellings" on the achilles tendons, which existed at that time:

". . . The tendons were found to be uniformly enlarged and rather spindle shaped, and there was a deposit of yellowish, almost orange-colored fatty tissue between the fiber and the tendons. About all that was performed at operation was the removal of enough of this tissue, which included both the fat and the tendon, to reduce them to normal size. To remove all the fatty tissue would have

TABLE 2.—*Summary of Blood Chemistry Values in Subject IV-2*

Date	Total Serum Cholesterol, Mg./100 Cc.	Total Serum Lipids, Mg./100 Cc.	Comment
1/30/49	640	.....	Patient received 500 cc. whole blood 1/31/49
2/ 4/49	615	.....	Patient placed on low fat and cholesterol diet
2/10/49	512	.....	
2/14/49	576	1,566	Control specimen obtained for choline investigation
.....	1,300	1,593	Sample obtained 4 hr. after ingestion of 50 cc. choline bicarbonate
2/15/49	946	1,513	Sample obtained 24 hr. after ingestion of choline
4/25/49	713	1,749	Eleven weeks since patient placed on diet

necessitated removing the entire tendons for a distance of probably 2 or 3 inches [5 or 7.5 cm.]. . . . The pathologic reports on the tissue removed at operation indicated fibrolipoma with fairly extensive fatty infiltration and degeneration of the heel cord. . . . Back of it all, there was rather an unusual family history. . . ."

It is interesting to note that the lesions of the heel cords at the time of writing were much larger than before the operation. At the time of the operation, the lesion was diffuse throughout the entire tendon. Ollerenshaw,[35] Lewis[36] and others reported that a tendon may be diffusely infiltrated by a xanthoma.

IV-4: The patient was a woman of 56. The blood pressure was 130 systolic and 80 diastolic. There were xanthomas on the extensor tendons of the hands and fusiform tuberous xanthomas (9.5 by 4 cm.) of the achilles tendons. No arcus senilis was noted; there was xanthelasma bilaterally. Several attacks of "crushing" pain in the chest had occurred, and the patient had had dyspnea for the "past few years." She had been "anemic for some time." The xanthomas of the achilles tendons developed at about the age of 7; at times, they had become very painful.

35. Ollerenshaw, R.: Giant-Celled Tumours of Tendon Associated with Xanthelasma, Brit. J. Surg. **10**:466-468 (April) 1923.

36. Lewis, D.: Tumors of the Tendon Sheaths, Surg., Gynec. & Obst. **59**:344-349 (Sept.) 1934.

Blood chemistry values on March 28, 1949 were as follows: total serum cholesterol, 276 mg., and total serum lipids, 1,970 mg. per hundred cubic centimeters.

IV-5: The subject was a man of 47. Tuberous xanthomas were observed on the extensor tendons of the hands and on the achilles tendons; there was no xanthelasma or arcus senilis, and no history of heart disease. Blood chemistry values on March 24, 1949 were as follows: total serum cholesterol, 444 mg., and total serum lipids, 1,375 mg. per hundred cubic centimeters.

IV-6: The patient, a man, died at 52. He had cancer of the stomach, but the family was told by their physician that he died of heart disease and not of the cancer. On several occasions, he had severe substernal pains.

Fig. 3.—Posterior view of lesions of xanthoma tuberosum on achilles tendons of subject V-2.

IV-7: The subject was a man of 52. The blood pressure was 120 systolic and 70 diastolic. No xanthomas were observed, and there was no arcus senilis and no history of dyspnea or angina pectoris. Blood chemistry values on March 28, 1949 were as follows: total serum cholesterol, 154 mg., and total serum lipids, 1,300 mg. per hundred cubic centimeters.

IV-8: This boy died at the age of 5 years of sarcoma of the stomach.

IV-9: The subject was a male of 51. No further information was available at the time of writing.

Generation V:V-1: This male subject was 36. The blood pressure was 124 systolic and 76 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 194 mg., and total serum lipids, 1,325 mg. per hundred cubic centimeters.

V-2: The patient was a woman of 30. The blood pressure was 128 systolic and 82 diastolic; fusiform tuberous xanthomas of the achilles tendons measuring approximately 10.5 by 4.5 cm., had been present since the age of 21 (figs. 3 and 4). There was no xanthelasma or arcus lipoides. On March 14, 1949 the patient had a sudden severe pain in the chest which necessitated hospitalization for five days. The pain was completely relieved by glyceryl trinitrate. Electrocardiograms were normal at that time. Studies of the blood, made on February 1, yielded the following data: red blood cells, 4,500,000; hemoglobin, 13.5 Gm. per hundred cubic centimeters; white blood cells, 8,000; differential count, normal; sedimentation rate, 7 mm. in one hour, and packed cell volume, 39 per cent. Blood chemistry values are listed in table 3.

Fig. 4.—Lateral view of lesions of xanthoma tuberosum on achilles tendon of subject V-2.

V-3: The subject was a man of 34. The blood pressure was 122 systolic and 78 diastolic. No xanthomas were observed; there was no arcus lipoides or history of heart disease. Studies of the blood on Feb. 1, 1949 showed the following: red blood cells, 4,800,000; hemoglobin, 14.2 Gm. per hundred cubic centimeters; white blood cells, 8,900; differential count, normal; sedimentation rate, 9 mm. in one hour, and packed cell volume, 40 per cent. Blood chemistry values were 325 mg. per hundred cubic centimeters for total serum cholesterol and 35 mg. for blood urea.

V-4: No information was available at the time of writing, other than that the subject was a female.

V-5: This subject was a girl of 16. The blood pressure was 116 systolic and 86 diastolic. On palpation, the achilles tendons were noted to be much thicker than one would expect in a girl of this age. She stated that there was occasionally

"something like a pain" sensation in them. No xanthomas were observed on the hands, elbows or eyelids. There was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 217 mg., and total serum lipids, 2,410 mg. per hundred cubic centimeters.

V-6: The subject was a woman of 27. The blood pressure was 120 systolic and 80 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 136 mg., and total serum lipids, 2,312 mg. per hundred cubic centimeters.

TABLE 3.—*Summary of Blood Chemistry Values in Subject V-2*

Date	Total Serum Cholesterol, Mg./100 Cc.	Total Serum Lipids, Mg./100 Cc.	Comment
8/16/48	448	.....	Patient placed on low fat and cholesterol diet
2/ 1/49	527	.....	Blood urea, 29 mg./100 cc.
2/ 5/49	645	.....	
2/ 9/49	401	1,231	Sample obtained 24 hours after ingestion of 50 cc. choline bicarbonate

TABLE 4.—*Summary of Blood Chemistry Determinations for 16 Persons in Family B*

Case	Sex	Age, Years	Total Serum Cholesterol, Mg./100 Cc.	Total Serum Lipids, Mg./100 Cc.	Comment
IV-2	F	62	512-1,300*	1,513-1,749*	Xanthomas; angina pectoris
IV-4	F	56	276	1,970	Xanthomas; angina pectoris
IV-5	M	47	444	1,375	Xanthomas
IV-7	M	52	154	1,300	
V-1	M	36	194	1,325	
V-2	F	30	401-645*	1,231	Xanthomas; angina pectoris
V-3	M	34	325	.....	Blood urea, 35 mg./100 cc.
V-5	F	16	217	2,410	
V-6	F	27	136	2,312	
V-7	M	30	148	1,835	
V-8	M	30	313	802	
V-9	M	29	201-262*	765-1,028*	
V-10	F	25	175	544	
V-11	M	20	169	1,662	
V-12	M	15	145	1,296	
VI-1	F	9	373	.....	

* Range of various samples.

V-7: The subject was a man of 30. The blood pressure was 102 systolic and 80 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 148 mg., and total serum lipids, 1,835 mg. per hundred cubic centimeters.

V-8: The subject was a man of 30. The blood pressure was 128 systolic and 70 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on Feb. 14, 1949: total serum cholesterol, 313 mg., and total serum lipids, 802 mg. per hundred cubic centimeters.

V-9: The subject was a man of 29. The blood pressure was 138 systolic and 86 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on April 5,

1949: total serum cholesterol, 201 mg., and total serum lipids, 765 mg. per hundred cubic centimeters. On April 25, the values had risen to 262 and 1,028 mg., respectively.

V-10: The subject was a woman of 25. The blood pressure was 120 systolic and 72 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on April 25, 1949: total serum cholesterol, 175 mg., and total serum lipids, 544 mg. per hundred cubic centimeters.

V-11: The subject was a youth of 20. The blood pressure was 122 systolic and 80 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows on March 28, 1949: total serum cholesterol, 169 mg., and total serum lipids, 1,662 mg. per hundred cubic centimeters.

V-12: The subject was a boy of 15. The blood pressure was 112 systolic and 76 diastolic. No xanthomas were observed, and there was no arcus lipoides or history of heart disease. Blood chemistry values were as follows: total serum cholesterol, 145 mg., and total serum lipids, 1,295 mg. per hundred cubic centimeters.

Generation VI:VI-1: The subject was a girl of 9; no xanthomas were observed, and there was no arcus lipoides or history of heart disease. The value for total serum cholesterol on Feb. 5, 1949 was 373 mg. per hundred cubic centimeters.

The information concerning both family A and family B was obtained principally from IV-2, IV-4 and IV-7 at different interviews. These people were active in genealogic work, which explains the exactness and scope of the information. I examined the genealogic records of the families.

Generations IV, V and VI are referred to as belonging to family B in comment on them.

COMMENT

Blood lipid studies showed that 15 of the 16 persons examined in family B had pronounced elevations of the level for total serum lipids, total serum cholesterol or both. No serum lipid studies were made on any members of family A. The blood chemistry determinations were done in duplicate under similar conditions by an experienced technician. Each value in the reported present article is an average of the two independent determinations made on that sample. Blood specimens from subjects IV-2 and V-2 were also analyzed in two different laboratories; the results were comparable to those obtained by the usual technician. The total serum cholesterol was determined by the method of Sperry and Brand [37] and the total lipids by the method of Wilson and Hanner.[38] The upper limits for "normal" values used were

37. Sperry, W. M., and Brand, F. C.: The Colorimetric Determination of Cholesterol, J. Biol. Chem. **150**:315-324 (Oct.) 1943.

38. Wilson, W. R., and Hanner, J. P.: Changes of Total Lipid and Iodine Number of Blood Fat in Alimentary Lipemia, J. Biol. Chem. **106**:323-330 (Aug.) 1934.

approximately 275 mg. per hundred cubic centimeters for total serum cholesterol and 800 mg. for total serum lipids.

Tuberous Xanthoma.—Six persons (III-10, IV-2, IV-3, IV-4, IV-5 and V-2) had tuberous xanthomas of the achilles tendons. Five of the 6 had a history of angina pectoris, and 4 had arcus senilis. It appears that at least in this family arcus senilis associated with disturbances in lipid metabolism does not develop until about the sixth decade of life.

Trauma has been mentioned as an etiologic agent in the formation of tuberous xanthoma, but this was not found to be so in family B or in the literature. The persons having tuberous xanthoma in this family claimed never to have had serious injuries to the achilles tendons. If the theory of trauma were valid, one would expect more men than women to have these lesions because of the greater hazards present in their occupational environment. Grenaud [39] compiled the reports of cases of xanthoma to 1927 and stated that the sex incidence was equal and that the time of appearance of the xanthoma was between birth and 40. The greatest number of occurrences were in patients aged from 3 to 6 years.

Swanson [40] stated that in cases of familial xanthoma cutaneous lesions may appear, or, more commonly, there may be a derangement of cholesterol metabolism giving rise to gallstones and atheromas. There is no history of members of either family having diabetes mellitus, jaundice (subject III-5 may have had it), disease of the gallbladder, disease of the kidneys, hypothyroidism or obesity.

Heart Disease.—Five members (II-5, II-8, III-11, III-13 and III-16) of family B died suddenly of heart disease. Three of these experienced severe pain in the chest before death. Four members (IV-2, IV-3, IV-4 and V-2) of family B living at the time of writing suffer from angina pectoris, and 2 deceased members (III-10 and IV-6) are known to have had angina pectoris. Three members (III-12, III-14 and III-15) died of a "slow kind" of heart disease in the sixth decade of life. Of the 4 remaining members represented in the pedigree chart as having heart disease, all died before the seventh decade of life. It is known that they had heart disease, but I was unable to obtain any specific information which would allow me to classify the type of cardiovascular disease. Two persons (II-9 and IV-1) who married into family B had heart disease.

The average age of death in family A was 72.2, whereas that in family B was 52.8. I have not included the subjects in family A who died young of infectious diseases, and I have excluded subjects I-3 and IV-8 because of certainty that they did not die of heart disease. Both

39. Grenaud, M.: Les xanthomes familiaux, Monde méd. **37**:725-731 (Aug. 1) 1927.

40. Swanson, J. C.: Familial Xanthomatosis, Brit. J. Dermat. **55**:289-293 (Dec.) 1943.

family A and family B lived in the same rural community. Their environment was the same, and their diets were similar (their activities, diet and environment were controlled to a great extent through their religious teachings). Thus, in two families living under very similar conditions, the average life expectancy was twenty years longer for one than for the other.

The inherited disturbances in lipid metabolism occurring in family B were, in general, of a benign nature until about midlife. At that time, the cardiovascular system seemed to be involved to such an extent that most of the members succumbed to what was apparently coronary heart disease. Similar observations were made in Norway by Müller.[9a] I was unable to determine whether the patients who died of the "slow type" of heart disease had myocardial or valvular involvement due to xanthomatous deposits, as reported by Török,[6] Low,[41] Cook and others,[42] Lenzen and Knauss,[43] and others, or had rheumatic heart disease.

I took blood pressure readings on 16 members of this family. None of them had hypertension; however, all but subject V-10 had hyperlipemia. Much investigation has been done in regard to the effect of elevated blood lipid levels (especially hypercholesteremia) on blood vessels and on their role in the formation of atherosclerosis. Two recent papers reviewed this problem in detail.[44]

Cancer.—Three members of family B (III-10, IV-6 and IV-8) died of cancer of the stomach. Much work has been done relating to cholesterol as a cause of, or a significant factor in, cancer. A few authors have reported cancer of the gastrointestinal system in patients with xanthomas,[45] but these reports are so uncommon in relation to the large number of reports of patients with xanthomatous lesions that one is led to believe that there is nothing in common between xanthomas and cancer.

Diet.—Much controversy has arisen over the probable effects of a diet high in cholesterol in the development of atherosclerosis. The

41. Low, R. C.: Xanthoma Tuberosum Multiplex, with Lesions in Heart and Tendon Sheaths, Brit. J. Dermat. **22**:109-118 (April) 1910.

42. Cook, C. D.; Smith, H. L.; Giesen, E. W., and Berdz, G. L.: Xanthoma Tuberosum, Aortic Stenosis, Coronary Sclerosis and Angina Pectoris, Am. J. Dis. Child. **73**:326-333 (March) 1947.

43. Lenzen, G., and Knauss, K.: Ueber Xanthoma multiplex planum, tuberosum, mollusciforme, Virchows Arch. f. path. Anat. **116**:85-104 (April) 1889.

44. Gubner, R., and Ungerleider, H. E.: Cholesterol Metabolism and Arteriosclerosis, Combined Staff Clinics, Am. J. Med. **6**:103-124 (Jan.) 1949; footnote 23.

45. Weidman, F. D., and Schaffer, H. W.: Xanthoma of the Skin and Larynx Associated with Carcinoma of the Stomach and a Regressive Xanthoma of the Pons, Arch. Dermat. & Syph. **35**:767-814 (May) 1937. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of an Intercurrent Zoster: Adenocarcinoma of the Ampulla of Vater at Necropsy, Arch. Int. Med. **59**:793-822 (May) 1937.

advocates of a low cholesterol diet, designed to prevent the development of arteriosclerosis, have based their opinions on the experimental production of atherosclerosis in the rabbit, the chicken and the dog. They have also pointed out that people living in areas where poor nutrition is prevalent supposedly have a low incidence of atherosclerosis. Gardner and Gainsborough [46] stated that there is no connection between the amount of sterol ingested and the cholesterol levels of the plasma during digestion. Chaikoff and his associates,[47] Turner and Steiner [48] and others were unable to produce any significant change in the serum cholesterol levels of "normal" persons by feeding them diets high in cholesterol. Steiner [49] reported on 35 patients given a high fat diet supplemented with 20 Gm. of cholesterol. Blood specimens were taken at 8 a. m. (fasting state), 10 a. m., noon and 4 p. m., and at 8 a. m. the following day. The results showed that little or no change in the serum cholesterol level occurred during the period, regardless of the ingestion of a large amount of cholesterol.

Subject IV-2 was placed on a low cholesterol and fat diet on Feb. 4, 1949. At that time she had a total serum cholesterol level of 615 mg. per hundred cubic centimeters. Blood specimens eleven weeks later showed a total serum cholesterol level of 713 mg., a rise of nearly 100 mg. (she had consumed no fats or cholesterol for thirty-six hours, and had eaten nothing for eighteen hours previous to the drawing of the second specimen. Subject V-2 was also placed on a restricted cholesterol diet for nearly six months, with no change whatsoever in the total serum cholesterol level. There were no changes in the size of the tuberous xanthomas in either of these subjects during their dietary periods. It seems apparent that diet has little or no effect on the serum lipid levels in normal persons or in those with a hereditary type of hyperlipemia (hypercholesteremia).

Heredity.—I have shown that six generations of family B had or had had heart disease and/or hyperlipemia. The inherited trait was a type of endogenous metabolic defect giving rise to high levels of serum lipids. The elevated blood lipid level in itself was unimportant clinically, as evidenced by the complete absence of symptoms in 11 members of the family having hyperlipemia. However, all 11 were under 36.

46. Gardner, J. A., and Gainsborough, H.: Studies on the Cholesterol Content of Normal Human Plasma, Biochem. J. **22**:1048-1056, 1928.

47. Chaikoff, I. L.; McGavack, T., and Kaplan, A.: The Blood Lipids in the Postabsorptive State and After the Ingestion of Fat in Normal Human Subjects and in a Case of Disseminated Cutaneous Xanthomata, J. Clin. Investigation **13**:1-13 (Jan.) 1934.

48. Turner, K. B., and Steiner, A.: A Long Term Study of the Variation of Serum Cholesterol in Man, J. Clin. Investigation **18**:45-49 (Jan.) 1939.

49. Steiner, A., in discussion on Cholesterol Metabolism and Arteriosclerosis,[47] pp. 117-120.

Xanthoma tuberosum, xanthelasma, arcus senilis, angina pectoris (presumably associated with coronary sclerosis) and possibly xanthomatous involvement of the myocardium and valves were complications arising from prolonged hyperlipemia in this family. In general, these complications arise in the fifth and sixth decades of life with the exception of xanthoma tuberosum, which usually occurs at an earlier age.

Fliegelman and his associates [50] stated the belief that the heterozygous alleles cause only hypercholesteremia, whereas the homozygous dominant condition is manifested not only as hypercholesteremia but also in the appearance of tuberous xanthomas and in cardiovascular changes. I have not found this to be so in my studies or elsewhere in the literature.[51]

Hyperlipemia in this family was transmitted as a simple autosomal dominant trait with complete penetrance.

Treatment.—The treatment of this condition is entirely symptomatic at the time of this report. Theoretically, some medicinal substance may be given to keep the serum cholesterol and other serum lipids at a normal level and thus eliminate the complications of prolonged hyperlipemia, but as yet no substance has been found which can achieve this for long periods. I gave choline bicarbonate to several members of family B for this purpose, but the results were inconclusive.

SUMMARY

A survey is presented on a family in which 15 members had hyperlipemia, 6 had xanthoma tuberosum and 18 had a history suggesting disease of the coronary arteries. Two factors were noted:

1. A disturbance in lipid metabolism was the basic inherited defect.
2. Hyperlipemia (hypercholesteremia) was inherited as a simple autosomal dominant trait.

The pertinent literature is reviewed.

ADDENDUM

After the completion of this study, a history of heart disease was obtained for 21 additional descendants of subjects I-3 and I-4. The ages of the subjects range from 7 to 61 years; 6 were under the age of 20. Over 200 members of this family remain to be studied.

Alvin J. Cox Jr., M.D., Windsor C. Cutting, M.D. and Donald E. King, M.D. gave technical advice in this study, and Miss Helen O'Connell, B.A., performed many of the serum lipid determinations.

50. Fliegelman, M. T.; Wilkinson, C. F., and Hand, E. A.: Genetics of Xanthoma Tuberosum Multiplex, Arch. Dermat. & Syph. **58**:409-429 (Oct.) 1948.

51. Boas and others.[5] Bloom, D.; Kaufman, S. R., and Stevens, R. A.: Hereditary Xanthomatosis, Arch. Dermat. & Syph. **45**:1-18 (Jan.) 1942.

Book Reviews

Hematology. By Cyrus C. Sturgis, M.D. Price, $12.50. Pp. 915. Springfield, Ill.: Charles C Thomas, 1948.

Dr. Sturgis' new text of hematology is an extremely personal book. In every section the material is presented in an intimate and informal manner which is much more reminiscent of a ward walk than a handbook. Hematology is a discipline which is greatly complicated by variations in nomenclature and terminology. Frequently this complexity leads to particularism and to a tendency for the students to concentrate on details and numbers and to neglect the broad view of the subject. It is also a discipline which has attracted clinical pathologists rather than internists; so that not infrequently attention has been directed mainly to technologic matters rather than to the patient as a sick person. The broad clinical experience and background of the author are apparent throughout this book. The periodical literature of hematology is very extensive, and much of it is contradictory and controversial. During the past eleven years Dr. Sturgis and his associates have prepared the annual reviews of hematology for the ARCHIVES. With this comprehensive bibliography at his disposal the author has been able to document his textbook in detail. The reviews have been objective, as a rule, and have presented all the recent work in the field. In his textbook, Dr. Sturgis has been much more critical and has attempted a just evaluation of the contributions that he cites.

The book is primarily clinical, and there are no chapters devoted to technical methods. All the major problems of clinical hematology are discussed, and the reviewer feels that the space assigned to each subject is adequate. A thorough historical review precedes the description of each of the principle blood dyscrasias. In a field which is developing as rapidly as hematology it is inevitable that some of the contemporary work will not be discussed. It is unfortunate that the recent studies of the Rh factor and of the use of exsanguination transfusion in the treatment of erythroblastosis fetalis could not have been included. Likewise, many readers would appreciate a presentation of Sturgis' opinions on the use of the nitrogen mustards and a more detailed discussion and evaluation of the employment of radioisotopes in the treatment of blood diseases.

The format of the book is pleasing, and the reviewer is heartily in favor of the practice of placing bibliographic references at the bottom of the pages on which they occur. The illustrations are generally good, and the tables and graphs are clear and adequate. This textbook is recommended for advanced students and for physicians interested in hematology. The mature clinical judgments, the excellent historical notes and the carefully selected bibliography should win a place for this book in the library of every hematologist.

Blood Clotting and Allied Problems. Transactions of the First Conference February 16-17, 1948, New York. Sponsored by the Josiah Macy Jr. Foundation, New York. Edited by Joseph E. Flynn. Price, $3.25. Pp. 179. New York: Josiah Macy Jr. Foundation, 1948.

Here is the first of a series of reports by groups of outstanding investigators in specified fields which are sure to become indispensable aids to true students of medicine. The careful selection of the contributors and the fundamental nature of their presentation will appeal to those readers who are seeking authentic, practical information. For instance, "Blood Clotting and Hemostasis" is presented by L. B. Jaques, of Canada, "Fibrinolytic Enzymes" by Tage Astrup of Copenhagen,

"Initiation and Acceleration Factors in Thrombosis" by K. M. Brinkhaus, "Protein Equilibrium Reactions in the Blood-Clotting Mechanism" by W. H. Seegers and A. G. Ware and "Dicoumarol and the Estimation of Prothrombin" by Karl Link, and there are others of equal importance. The discussion of the papers by the other members of the group adds great interest and clarification.

In an extensive appendix the exact procedures for prothrombin determinations which are carried out in the various laboratories of several of the participants are given. The contributors to this section include, among others, Quick, Tocontins, Seegers, Barker, of the Mayo Clinic, and Brambel, of Toronto.

This report will be eagerly received by laboratory directors, clinicians and medical investigators who are anxious to increase their understanding of this difficult subject and the accuracy of their laboratory technics.

Le fond d'oeil des hypertendus et des cyanoses. By Daniel Routier, M.D. Pp. 100, with 232 illustrations. Paris: Masson & Cie, Editeurs Libraires de l'Academie de Medecine, 1947.

The author, who is a cardiologist, presents in black and white 232 photographs of the fundus of the eye, each picture accompanied with brief notes regarding the clinical condition of the patient and pointing out the noteworthy changes in the retina and retinal vessels. He used a Nordenson camera at exposures of one tenth to one twenty fifth of a second, with about the success that others have had with this somewhat unsatisfactory instrument, some of his photographs being good and others only fair.

In the first chapter he describes and illustrates the normal fundus, and in the second he presents the generally recognized vascular and retinal changes of hypertensive disease. Some would take exception to his emphasis on tortuosity of retinal vessels as evidence of hypertension. He stresses the significance of local spasms of the retinal arterioles and notes that they may persist for many months, and he rightly points to these changes and to the small exudates as having greater significance than have some of the gross changes which are more readily seen.

A chapter on interpretation deals with the origin of retinal edema and of various types of exudates and is an excellent summary of present opinion on the subject. A final chapter illustrates cases of congenital and acquired cyanosis.

Psychiatry in General Practice. By Melvin W. Thorner, M.D., D.Sc. Price, $8. Pp. 659. Philadelphia: W. B. Saunders Company, 1948.

In the past a wide gap has separated the psychiatrist and the rest of the medical profession. This is unfortunate because, in practically every instance, the family physician sees the patient first and, in the long run, is required to treat more mentally ill patients in the stage when treatment short of shock therapy may be effective than the psychiatrist. Dr. Thorner's book, "Psychiatry in General Practice," as stated in his preface, "is an attempt to lift psychiatry out of the realm of terra incognita for those whose primary efforts are spent in other fields. . . . Only by removing the aura of mystery from the practice of psychiatry, can psychiatry be rendered a useful tool in the hands of those who deal with the greatest number of psychiatric patients."

One cannot help but agree with Dr. C. C. Burlingame in his foreword when he points out that "to an astonishing degree, the author of this book has overcome the psychiatric language barrier." The clear presentation of psychiatric problems, with short, illustrative case histories and without long, abstract discussions full of the catch words and theoretic claptrap of so much of the present day writing

on this subject, is, indeed, refreshing. The book is cheerfully recommended to the uninitiated who up to this time—with some justification—have regarded psychiatrists and their specialty with some suspicion and alarm.

Mayo Clinic Diet Manual. By the Committee on Dietetics of the Mayo Clinic. Price, $4. Pp. 329. Philadelphia: W. B. Saunders Company, 1940.

This is an excellent manual. The material was originally prepared for use in teaching and in planning the diets of patients at the Mayo Clinic; it was put into its present printed form in answer to requests from physicians and from other institutions. It represents the convergent trend but not necessarily unanimity of opinion. Because of the rapid headway being made in the science of nutrition, frequent revised printings are contemplated.

The manual consists of a comprehensive series of dietary tables with a minimum of explanatory notes. It is well planned for easy reference, and the physician can find in it a detailed outline of practically any dietary regimen he may need. It is concise, and the foods are prescribed in household measures.

A few of the dietary patterns appear to the reviewer to be faulty in minor details, such as the relatively large proportion of cream in the milk-cream mixture used for peptic ulcer (1:1) and the conservatism with which protein is prescribed, as well as the liberal amount of fat allowed, in diseases of the liver. On the whole, however, these diets will appeal to the physician and to the nutritionist as being eminently suitable. The pragmatic test, based on the theory that practical results are the sole test of truth, has been applied: These diets have all been evaluated on the results of clinical trial. The teacher of nutrition as well as the physician in practice will find the manual a valuable aid.

Textbook of the Rheumatic Diseases. Edited by W. S. C. Copeman, O.B.E., M.D., F.R.C.P. Price, $12.50. Pp. 612, with 351 illustrations. Baltimore: The Williams & Wilkins Company, 1948.

This beautifully printed and profusely illustrated book is a cooperative effort on the part of some two dozen British physicians to cover comprehensively the subject of the "rheumatic diseases." Introductory chapters on history, anatomy and physiology of pain and anatomy and physiology of joints give some idea of the thoroughness of the approach. The various rheumatic diseases are then taken up systematically, with final sections on such specific topics as the radiology of rheumatic disease, radiotherapy, physiotherapy and psychiatric aspects. Each section is followed by a bibliography, many of them comprehensive. Most of the discussions are adequate, although that on rheumatic fever, comprising only 10 in a book of some 600 pages, seems perhaps too brief; however, further material on this most important "disease" is given later in the volume. The illustrations, some in color, and the reproductions of roentgenograms are outstanding. The book is certainly a landmark on the subject, and our British colleagues have done themselves proud in producing such an outstanding compilation.

Fundamentals of Pulmonary Tuberculosis. By Edward W. Hayes, M.D. Price, $9.50. Pp. 480, with 79 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1949.

"The purpose of this book is to present in as few concise chapters as possible the fundamentals pertaining to the cause, the prevention, the diagnosis, the treatment and the control of tuberculosis." These aims are achieved in twenty-six chapters, written by twenty-seven experts in the field of tuberculosis.

In spite of the large number of contributors to this book, the editor has kept repetitious discussion to a minimum.

Although certain chapters inevitably stand out in a volume of this type, most of the fundamental aspects of tuberculosis are satisfactorily discussed. Due to the progress that is being made from month to month in the antibacterial therapy of tuberculosis, it would be impossible for the chapter on this subject to contain the latest developments. However, the earlier discoveries are reviewed, and the proper use of streptomycin is described in detail.

The book has been prepared for "the medical student, the practicing physician, and the medical teacher," and each of them will find it to be a satisfactory review of the various aspects of pulmonary tuberculosis.

Shock and Allied Forms of Failure of the Circulation. By H. A. Davis, M.D., C.M., F.A.C.S. Price, $12. Pp. 608, with 55 illustrations. New York: Grune & Stratton, Inc., 1949.

This volume is an ideal book in regard to size, binding, format and printing. For an initial work it appears to be singularly free from typographical errors. In spite of these excellent physical aspects the book is difficult to read, owing to the almost encyclopedic character of the subject material. The author has made an extensive review of the literature on both experimental and clinical work pertaining to shock and to shocklike states. In addition, he presents a considerable amount of data based on his own researches and observations. Although the review of the literature is not complete on some minor aspects of the subject, a compilation of all the references cited at the end of each chapter would probably represent the most complete index of articles on acute circulatory failure in existence. The book is a valuable addition to medical literature and should prove to be especially useful to investigators working on problems related to acute failure of the circulation.

Roentgen Studies of the Lungs and Heart. A series of lectures delivered at the center for continuation study. Edited by Leo G. Rigler, M.D. Price, $7. Pp. 216, with 98 illustrations. Minneapolis: University of Minnesota Press, 1948.

This series of lectures delivered at the University of Minnesota by Westermark summarizes his methods for study of the heart and lungs. The use of controlled intrapulmonary respiratory pressure, positive and negative, for the study of pulmonary lesions is particularly interesting. The early diagnosis of bronchogenic carcinoma, the identification of localized as well as generalized emphysema and the discussion of pulmonary embolism and infarction and of roentgen cinematography to observe hemodynamics are included and should prove to be of value to roentgenologists, phthisiologists and cardiologists. The text is accompanied by many illustrations, but unfortunately the accompanying legends are relatively incomplete and poorly written. Since the illustrations are so numerous, more detailed legends and labeling would have been of considerable value to the average reader.

Neutron Effects on Animals. By the Staff of the Biochemical Research Foundation (Dr. Ellice McDonald, Director). Price, $3. Pp. 198. Baltimore: The Williams and Wilkins Company, 1947.

Nearly a score of investigators contributed to this volume, the chapters of which resemble separate publications such as might be found in almost any periodical dealing with the medical sciences. The material consists of detailed

reports concerning a great variety of findings after irradiation with neutrons; the methods and doses employed are described fully. Experimental animals included dogs, rabbits, rats, mice and chickens; plants and micro-organisms were also used. The effects of irradiation under consideration range from those on mortality, body weight, growth and "clinical" behavior to those on formed elements and sedimentation rate of the blood, ordinary "blood chemistry," gastric juice, enzymes, histologic appearances, neoplasm induction and electrophoresis of plasma and homogenized bone marrow.

Child Psychiatry. By Leo Kanner, M.D. Enlarged second edition. Price, $8.50. Pp. 776. Springfield, Ill.: Charles C Thomas, 1949.

Dr. Kanner's work on child psychiatry at Johns Hopkins Hospital is too well known to require much introduction. The handsome volume just issued embodies his latest and carefully considered views on the subject. No aspect of child psychiatry has been left untouched. The general background is developed, the relation of physical ills to mental reactions is discussed and finally the psychiatric disturbances in the stricter sense are taken up. Although the book is a large one, the subject is so great that one almost has a feeling of sketchiness here and there; some of the sections on therapy especially seem almost too brief. Dr. Kanner (and this cannot be said of all psychiatrists) writes vividly and intelligibly; his book no doubt remains the standard text on this subject.

Annual Review of Physiology (Volume XI), 1949. By Victor E. Hall. Price, $6.00. Pp. 643. Stanford University, Calif.: Annual Reviews, Inc., 1949.

Included in this book are reviews of work in the fields of developmental physiology, neurophysiology, physiologic psychology, radiation and pharmacology, and of work on the reproductive system, the metabolic functions of the endocrine system, the liver, the digestive system, the hearing, the vision, the muscles, the lymphatic system, the heart, the peripheral circulation, the respiration, the kidneys, hematopoiesis and permeability. Each reviewer has attempted to present the pertinent, rather than all, recent contributions related to his subject. Nevertheless, over 4,300 references are included. The volume is a well organized and concise survey. It offers the scientifically trained reader a valuable and practical means of keeping abreast of basic physiologic investigation.

Histopathology of the Peripheral and Central Nervous Systems. By George B. Hassin, M.D. Third edition. Price, $8.50. Pp. 612, with 325 illustrations. Hamilton, Ill.: The Hamilton Press, 1948.

Dr. Hassin's book first appeared in 1933, and the present edition (1948) is the third one. The author has turned publisher in this case, and the work appears under his own imprint. It is well printed on fine paper, and the numerous illustrations are excellently reproduced. Dr. Hassin is well known as an authority on neurohistology, and wherever one turns in this book he finds a precise and clear discussion. There are extensive bibliographies, and the book will continue as in the past to be a valuable text and reference book.

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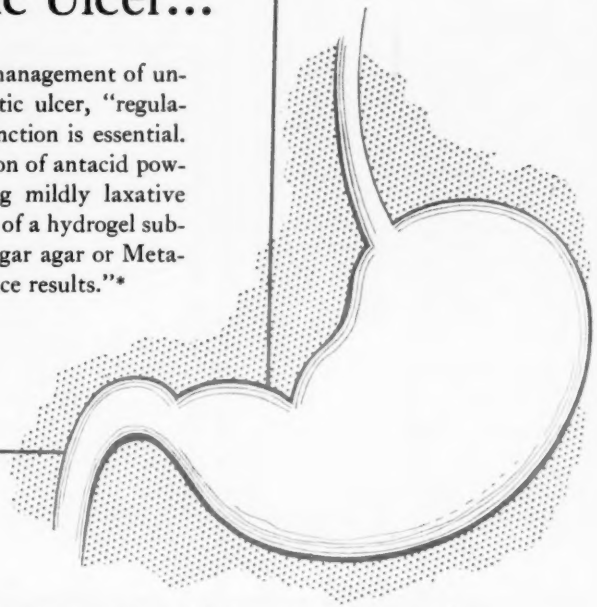

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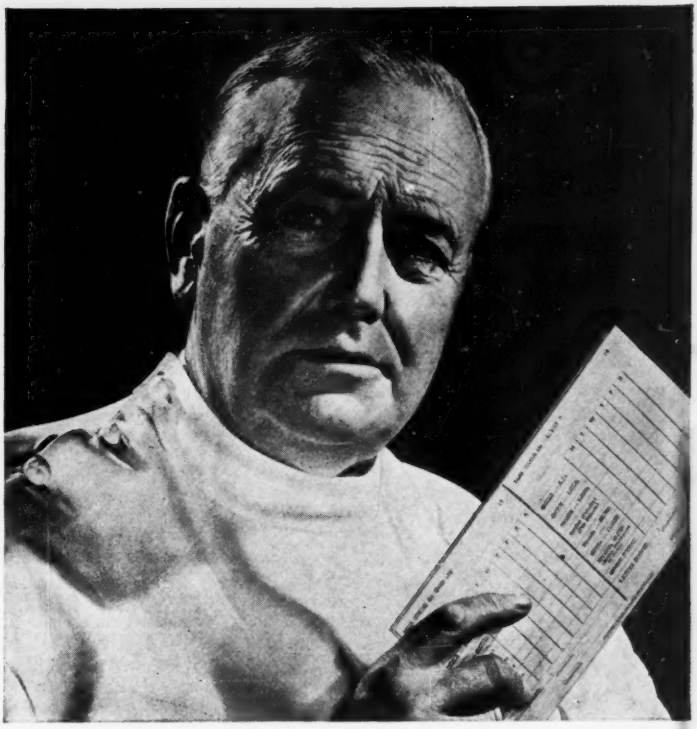

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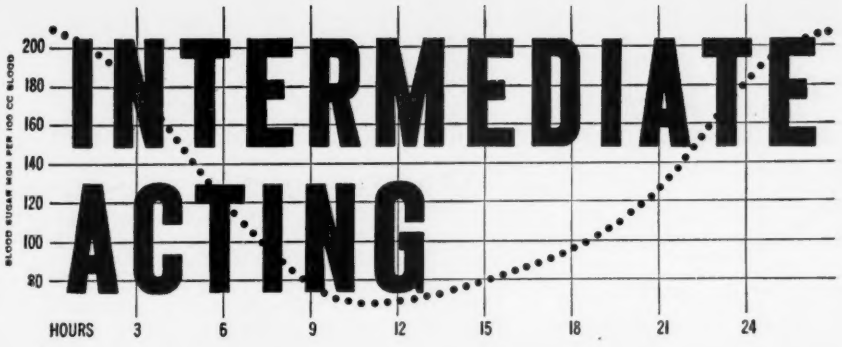

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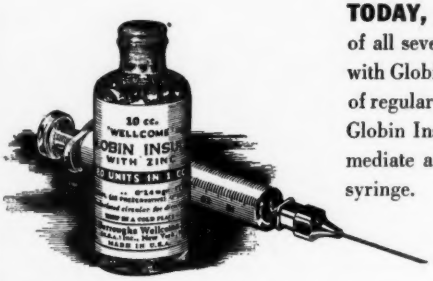

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